

=> b reg
FILE 'REGISTRY' ENTERED AT 14:43:45 ON 21 JUN 2005
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 20 JUN 2005 HIGHEST RN 852602-49-4
DICTIONARY FILE UPDATES: 20 JUN 2005 HIGHEST RN 852602-49-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d ide 17 tot

L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 9046-27-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN α-Glutamyltranspeptidase
CN γ-Glutamyl peptidyltransferase
CN γ-Glutamyl transpeptidase
CN γ-Glutamyl transpeptidase-related enzyme
CN γ-Glutamyltransferase
CN γ-GPT
CN γ-GT
CN γ-GTP
CN E.C. 2.3.2.2
CN L-γ-Glutamyl transpeptidase
CN L-γ-Glutamyltransferase
CN L-Glutamyltransferase
DR 9013-62-1
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CABA,
CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, CSNB, IFICDB, IFIPAT,
IFIUDB, MSDS-OHS, NAPRALERT, NIOSHTIC, PROMT, TOXCENTER, USPAT2,
USPATFULL
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

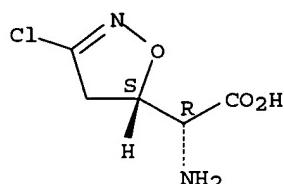
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
8426 REFERENCES IN FILE CA (1907 TO DATE)

14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 8438 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d ide l10 tot

L10 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 676551-24-9 REGISTRY
 ED Entered STN: 23 Apr 2004
 CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 (α R,5S)- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C5 H7 Cl N2 O3
 SR CA
 LC STN Files: CA, CAPLUS

Absolute stereochemistry.

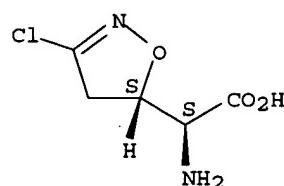


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 161922-40-3 REGISTRY
 ED Entered STN: 04 Apr 1995
 CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C5 H7 Cl N2 O3 . Cl H
 SR CA
 LC STN Files: CA, CAPLUS
 CRN (42228-92-2)

Absolute stereochemistry.



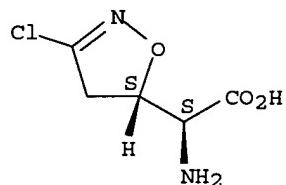
● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 105116-13-0 REGISTRY
 ED Entered STN: 08 Nov 1986

CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
monohydrochloride, (R*,R*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
monohydrochloride, (R*,R*)-(\pm)-
FS STEREOSEARCH
MF C5 H7 Cl N2 O3 . Cl H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)
CRN (76898-56-1)

Relative stereochemistry.

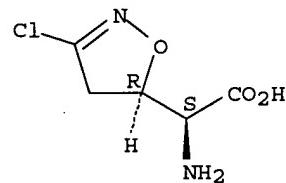


● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 104832-77-1 REGISTRY
ED Entered STN: 25 Oct 1986
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-, (R*,S*)-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
(R*,S*)-(\pm)-
FS STEREOSEARCH
MF C5 H7 Cl N2 O3
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.



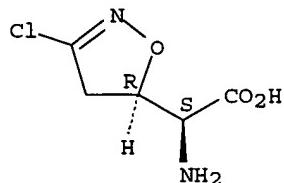
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 104832-76-0 REGISTRY
ED Entered STN: 25 Oct 1986

CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
monohydrochloride, (R*,S*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
monohydrochloride, (R*,S*)-(\pm)-
FS STEREOSEARCH
MF C5 H7 Cl N2 O3 . Cl H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)
CRN (104832-77-1)

Relative stereochemistry.

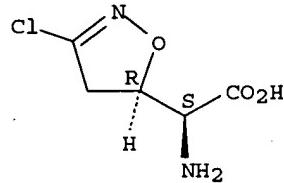


● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 80184-13-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
(α S,5R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-, [R- (R*,S*)]-
FS STEREOSEARCH
MF C5 H7 Cl N2 O3
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 76898-56-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-, (R*,R*)-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 (R*,R*)-(\pm)-

OTHER NAMES:

CN (\pm)-Acivicin

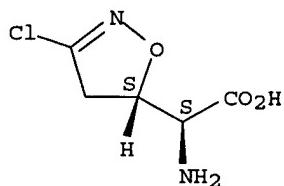
FS STEREOSEARCH

MF C5 H7 Cl N2 O3

CI COM

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
 (*File contains numerically searchable property data)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
 4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN

RN 52583-41-2 REGISTRY

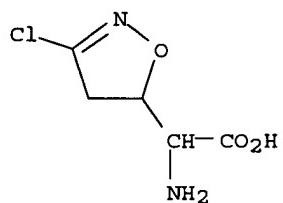
ED Entered STN: 16 Nov 1984

CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro- (9CI) (CA INDEX NAME)

FS 3D CONCORD

MF C5 H7 Cl N2 O3

LC STN Files: BEILSTEIN*, CA, CANCERLIT, CAPLUS, MEDLINE, NIOSHTIC,
 TOXCENTER
 (*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN

RN 42228-92-2 REGISTRY

ED Entered STN: 16 Nov 1984

CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 (α S,5S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-, [S-(R*,R*)]-

OTHER NAMES:

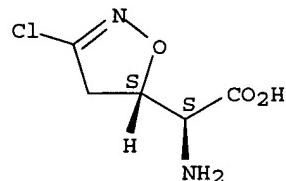
CN (α -S, 5S)- α -Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid

CN Acivicin

CN Antibiotic AT 125

CN AT 125
 CN NSC 163501
 CN U 42126
 FS STEREOSEARCH
 MF C5 H7 Cl N2 O3
 CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
 BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM,
 DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MSDS-OHS, NAPRALERT,
 NIOSHTIC, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN,
 USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: WHO

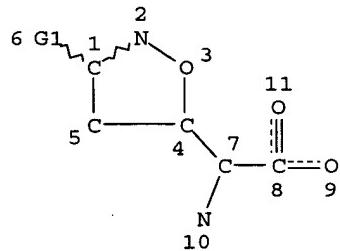
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

302 REFERENCES IN FILE CA (1907 TO DATE)
 13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 302 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d que sta 115
L13 STR



VAR G1=O/X
 NODE ATTRIBUTES:
 NSPEC IS RC AT 10
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
 L15 119 SEA FILE=REGISTRY SSS FUL L13

100.0% PROCESSED 209 ITERATIONS
 SEARCH TIME: 00.00.01

119 ANSWERS

=> d his full

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(FILE 'HOME' ENTERED AT 13:08:51 ON 21 JUN 2005)

FILE 'HCAPLUS' ENTERED AT 13:57:10 ON 21 JUN 2005
L1      1 SEA ABB=ON PLU=ON US20040115284/PN OR (EP2000-107406# OR
          WO2002-EP1799#)/AP, PRN

FILE 'REGISTRY' ENTERED AT 13:58:13 ON 21 JUN 2005

FILE 'HCAPLUS' ENTERED AT 13:58:16 ON 21 JUN 2005
L2      TRA L1 1- RN :      35 TERMS

FILE 'REGISTRY' ENTERED AT 13:58:16 ON 21 JUN 2005
L3      35 SEA ABB=ON PLU=ON L2

FILE 'WPIX' ENTERED AT 13:58:18 ON 21 JUN 2005
L4      2 SEA ABB=ON PLU=ON US20040115284/PN OR (EP2000-107406# OR
          WO2002-EP1799#)/AP, PRN

FILE 'REGISTRY' ENTERED AT 14:19:59 ON 21 JUN 2005
L5      1 SEA ABB=ON PLU=ON L3 AND ACIVICIN#
L6      2 SEA ABB=ON PLU=ON L3 AND GAMMA
L7      1 SEA ABB=ON PLU=ON L6 AND ?TRANSFER?/CNS
L8      494 SEA ABB=ON PLU=ON ((GAMMA (1A) (GT# OR GLUTAMYLPEPTIDAS? OR
          GLUTAMYLTRANSFERAS? OR GLUTAMYL (1A) (?PEPTIDAS? OR ?TRANSFERAS
          E?)))/CNS
L9      11 SEA ABB=ON PLU=ON C5H7CLN2O3 AND NOC3/ES
L10     9 SEA ABB=ON PLU=ON L9 NOT (ACETAMIDE OR COMPD OR COMPOUND)
L11     STR
L12     6 SEA SSS SAM L11
L13     STR L11
L14     8 SEA SSS SAM L13
L15     119 SEA SSS FUL L13
          SAV TEM HAR325F0/A L15

FILE 'HCAPLUS' ENTERED AT 14:48:05 ON 21 JUN 2005
L16     14574 SEA ABB=ON PLU=ON (L7 OR L8)
L17     15976 SEA ABB=ON PLU=ON GLUTAMYLTRANSFERAS? OR GLUTAMYLPEPTIDAS?
          OR GLUTAMYLTRANSPEPTIDAS? OR GAMMA (1A) (GT# OR GPT OR GLUTAM?
          (1A) (?PEPTIDAS? OR ?TRANSFERAS?)) OR "EC2.3.2.2" OR "E.C.2.3.2.
          2" OR (EC OR E (1A) C) (1A)"2.3.2.2"
L18     307 SEA ABB=ON PLU=ON L10 OR L10/D
L19     502 SEA ABB=ON PLU=ON ISOXZOLACET? (1A) ACID (1A) AMINO (1A) CHLORO
          (2A) (DIHYDRO OR DI (1A) HYDRO) OR ACIVICIN# OR AT125 OR
          AT(1A)125 OR NSC163501 OR NSC(1A) (163501 OR 163 (1A) 501) OR
          U42126 OR U(1A) (42126 OR 42 (1A) 126)
L20     349 SEA ABB=ON PLU=ON L15
          E CHRONIC RENAL DISEASE/CT
          E E3+ALL
          E KIDNEY, DISEASE/CT
          E KIDNEY, DISEASE/CT
          E E3+ALL
L21     6301 SEA ABB=ON PLU=ON "KIDNEY, DISEASE"+OLD,NT/CT (L) CHRONIC?
          E GLOMERULOSCL/CT
          E E5+ALL
L22     1409 SEA ABB=ON PLU=ON "KIDNEY, DISEASE"+OLD,NT/CT (L) ?GLOMERULOS
          CLER?

FILE 'REGISTRY' ENTERED AT 15:05:48 ON 21 JUN 2005
L23     2 SEA ABB=ON PLU=ON L3 AND OXYGEN

FILE 'HCAPLUS' ENTERED AT 15:06:26 ON 21 JUN 2005
          E WEIHER H/AU
L24     32 SEA ABB=ON PLU=ON ("WEIHER H"/AU OR "WEIHER HANS"/AU)
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L25 E SIES H/AU
 826 SEA ABB=ON PLU=ON ("SIES H"/AU OR "SIES HELMUT"/AU)
 E WAGNER G/AU
 L26 1692 SEA ABB=ON PLU=ON ("WAGNER G"/AU OR "WAGNER G A"/AU OR
 "WAGNER G A II"/AU OR "WAGNER G A III"/AU OR "WAGNER G B"/AU
 OR "WAGNER G C"/AU OR "WAGNER G CHRIST"/AU OR "WAGNER G D"/AU
 OR "WAGNER G D JR"/AU OR "WAGNER G DONALD"/AU OR "WAGNER G
 E"/AU OR "WAGNER G E JR"/AU OR "WAGNER G F"/AU OR "WAGNER G
 G"/AU OR "WAGNER G GALE"/AU OR "WAGNER G H"/AU OR "WAGNER G
 J"/AU OR "WAGNER G L"/AU OR "WAGNER G LOUIS"/AU OR "WAGNER G
 M"/AU OR "WAGNER G N"/AU OR "WAGNER G P"/AU OR "WAGNER G R"/AU
 OR "WAGNER G S"/AU OR "WAGNER G W"/AU)
 E WAGNER GUNTER/AU
 L27 104 SEA ABB=ON PLU=ON ("WAGNER GUNTER"/AU OR "WAGNER GUNTER
 P"/AU OR "WAGNER GUNTHER"/AU OR "WAGNER GUNTHIER A"/AU OR
 "WAGNER GUNTHIER W"/AU)
 L28 1 SEA ABB=ON PLU=ON (GTX (1A) PHARM?)/CS, PA
 L29 5 SEA ABB=ON PLU=ON (L16 OR L17) AND L22
 L30 27 SEA ABB=ON PLU=ON (L16 OR L17) AND L21
 L31 2 SEA ABB=ON PLU=ON (L29 OR L30) AND (L24 OR L25 OR L26 OR L27
 OR L28)
 L32 3 SEA ABB=ON PLU=ON L29 NOT L31
 L33 0 SEA ABB=ON PLU=ON L32 AND (L18 OR L19 OR L20)
 L34 25 SEA ABB=ON PLU=ON L30 NOT (L29 OR L31)
 L35 0 SEA ABB=ON PLU=ON L34 AND (L18 OR L19 OR L20)
 E NEPROSIS/CT
 E NEPHROSIS/CT
 E E3+ALL
 L36 421 SEA ABB=ON PLU=ON "KIDNEY, DISEASE"+OLD,NT/CT AND (L16 OR
 L17)
 L37 11 SEA ABB=ON PLU=ON L36 AND (L18 OR L19 OR L20)
 L38 2 SEA ABB=ON PLU=ON L37 AND (L24 OR L25 OR L26 OR L27 OR L28)
 L39 9 SEA ABB=ON PLU=ON L37 NOT L38
 L40 5729 SEA ABB=ON PLU=ON (L16 OR L17) (L) (INHIB? OR BLOCK? OR
 ANTAGON?)
 L41 2417 SEA ABB=ON PLU=ON GGT
 L42 377 SEA ABB=ON PLU=ON L41 (L) (INHIB? OR BLOCK? OR ANTAGON?)
 L43 57 SEA ABB=ON PLU=ON (L41 OR L42) AND (L21 OR L22 OR "KIDNEY,
 DISEASE"+OLD,NT/CT)
 L44 2 SEA ABB=ON PLU=ON L43 AND (L18 OR L19 OR L20)
 L45 1 SEA ABB=ON PLU=ON L44 AND (L24 OR L25 OR L26 OR L27 OR L28)
 L46 1 SEA ABB=ON PLU=ON L44 NOT L45
 L47 QUE ABB=ON PLU=ON PY<=2001 OR AY<2001 OR AY<=2001 OR
 PD<20010220 OR AD<20010220 OR PRD<20010220
 L48 4 SEA ABB=ON PLU=ON L32 OR L46
 L49 3 SEA ABB=ON PLU=ON L48 AND L47
 L50 4 SEA ABB=ON PLU=ON (L48 OR L49)
 L51 2 SEA ABB=ON PLU=ON L34 AND L40
 L52 QUE ABB=ON PLU=ON REACT? (1A) (OXYGEN OR O2)
 L53 159 SEA ABB=ON PLU=ON (L21 OR L22) AND L52
 E REACTIVE OXYGEN/CT
 E E4+ALL
 L54 24862 SEA ABB=ON PLU=ON REACTIVE OXYGEN SPECIES/CT
 L55 130 SEA ABB=ON PLU=ON (L21 OR L22) AND L54
 L56 2 SEA ABB=ON PLU=ON (L53 OR L55) AND (L16 OR L17 OR L40 OR
 L42)
 L57 2 SEA ABB=ON PLU=ON (L53 OR L55) AND (L18 OR L19 OR L20)
 L58 2 SEA ABB=ON PLU=ON L56 AND (L18 OR L19 OR L20)
 L59 2 SEA ABB=ON PLU=ON (L56 OR L57 OR L58) AND (L24 OR L25 OR L26
 OR L27 OR L28)
 E GUMERULOPATH/CT
 E GLUMERULOPATH/CT
 E GLOMERULOPATH/CT
 E E3+ALL
 E E4+ALL
 L60 QUE ABB=ON PLU=ON "KIDNEY, DISEASE"+OLD,NT/CT

L61 9392 SEA ABB=ON PLU=ON L60 (L) ?GLOMERUL?
 E NEUROPATHY/CT
 E E3+ALL
 E NERVE, DISEASE/CT
 E E3+ALL
L62 2308 SEA ABB=ON PLU=ON "NERVE, DISEASE"+OLD,NT/CT (L)NEUROP? (L)
 ?DIABET?
L63 48 SEA ABB=ON PLU=ON (L61 OR L62) AND (L16 OR L17 OR L40 OR
 L42)
L64 2 SEA ABB=ON PLU=ON L63 AND (L18 OR L19 OR L20)
L65 2 SEA ABB=ON PLU=ON L64 AND (L24 OR L25 OR L26 OR L27 OR L28)
L66 278 SEA ABB=ON PLU=ON (L16 OR L17 OR L40 OR L42) AND (L18 OR L19
 OR L20)
 E DISEASES/CT
 E E3+ALL
 E E2
 E E3+OLD,NT1
L67 37301 SEA ABB=ON PLU=ON ("DISEASE, ANIMAL"+OLD,NT1/CT OR DISEASE?/C
 W) (L) (CHRONIC? OR ?DEGEN?)
L68 2 SEA ABB=ON PLU=ON L66 AND L67
L69 1 SEA ABB=ON PLU=ON L68 AND (L24 OR L25 OR L26 OR L27 OR L28)
L70 1 SEA ABB=ON PLU=ON L68 NOT L69
L71 23 SEA ABB=ON PLU=ON ("DISEASE, ANIMAL"+OLD,NT1/CT OR DISEASE?/C
 W) AND L66
L72 2 SEA ABB=ON PLU=ON L71 AND (L24 OR L25 OR L26 OR L27 OR L28)
L73 21 SEA ABB=ON PLU=ON L71 NOT L72
L74 14 SEA ABB=ON PLU=ON L73 AND L47
L75 3 SEA ABB=ON PLU=ON (L18 OR L19 OR L20) (L) (PAC OR THU OR
 BIOL+NT)/RL AND L74
L76 2 SEA ABB=ON PLU=ON L31 OR L38 OR L45 OR L59 OR L65 OR L69 OR
 L72
L77 9 SEA ABB=ON PLU=ON L50 OR L51 OR L75

=> b hcap

FILE 'HCAPLUS' ENTERED AT 15:50:34 ON 21 JUN 2005
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FILE COVERS 1907 - 21 Jun 2005 VOL 142 ISS 26
 FILE LAST UPDATED: 20 Jun 2005 (20050620/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all fhitstr 176 tot

L76 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2002:657961 HCAPLUS
 DN 137:195608
 ED Entered STN: 30 Aug 2002
 TI Use of γ -glutamyl transpeptidase (.

gamma.-GT) inhibitors for the treatment of degenerative diseases

IN Weiher, Hans; Sies, Helmut; Wagner, Gunter
 PA GTX Pharmaceuticals G.m.b.H., Germany
 SO PCT Int. Appl., 28 pp.
 CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K038-06
 ICS A61P027-16; A61P013-00

CC 1-12 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002066047	A1	20020829	WO 2002-EP1799	20020220
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1361885	A1	20031119	EP 2002-718150	20020220
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004115284	A1	20040617	US 2003-644325	20030819
PRAI	EP 2001-104063	A	20010220		
	EP 2000-107406	A	20010220		
	WO 2002-EP1799	W	20020220		

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
	WO 2002066047	ICM	A61K038-06
		ICS	A61P027-16; A61P013-00
	WO 2002066047	ECLA	A61K038/06A
	US 2004115284	NCL	424/649.000; 514/037.000; 514/012.000; 514/018.000; 514/064.000; 514/457.000
		ECLA	A61K031/704; A61K038/06

AB The invention discloses the use of γ -GT inhibitors for the preparation of a pharmaceutical composition for the treatment of a degenerative disease, in particular of chronic renal diseases or inner ear degenerative diseases.

ST degenerative disease treatment gamma glutamyl transpeptidase inhibitor; chronic renal disease treatment gamma glutamyl transpeptidase inhibitor; ear degenerative disease treatment gamma glutamyl transpeptidase inhibitor

IT Glycosides
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (amino, sensorineural deafness induced by; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
 (chronic; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Disease, animal
 (degenerative; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
 (diabetic nephropathy; γ -glutamyl

transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(focal glomerulosclerosis; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(glomerulosclerosis, segmental; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(glomerulus, autoimmune; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(glomerulus, inflammatory; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Anti-inflammatory agents
Inflammation
(inflammatory glomerulonephropathy; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Ear
(inner, degenerative condition or injury; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(minimal change nephrosis; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligopeptides; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Ear, disease
(otosclerosis; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Aging, animal
Drugs
Metabolism
Physiology, animal
(sensorineural deafness induced by; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Deafness
(sensorineural; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Antioxidants
Drug delivery systems
Fibroblast
Peptidomimetics
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Reactive oxygen species
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Anilides
Peptides, biological studies
Proteins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
 (γ -glutamyl transpeptidase
 inhibitors for treatment of degenerative diseases)

IT 70-18-8D, Glutathione, analogs
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (peptidomimetic; γ -glutamyl
 transpeptidase inhibitors for treatment of
 degenerative diseases)

IT 15663-27-1D, Cisplatin, derivs.
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (sensorineural deafness induced by; γ -glutamyl
 transpeptidase inhibitors for treatment of
 degenerative diseases)

IT 453650-49-2 453650-50-5 453650-51-6 453650-52-7 453650-53-8
 453650-54-9 453650-55-0 453650-56-1 453650-57-2 453650-58-3
 453650-59-4 453650-60-7 453650-61-8 453650-63-0 453650-64-1
 453650-65-2 453650-66-3 453650-67-4 453650-68-5 453650-69-6
 453650-70-9 453650-71-0
 RL: PRP (Properties)
 (unclaimed sequence; use of γ -glutamyl
 transpeptidase (γ -GT)
 inhibitors for the treatment of degenerative diseases)

IT 70-18-8, Glutathione, biological studies 7782-44-7D, Oxygen,
 reactive species 9001-05-2, Catalase 9001-48-3, GSSG reductase
 9013-66-5, Glutathione peroxidase 9046-27-9, γ -
 Glutamyl transpeptidase 9054-89-1, Superoxide
 dismutase 11062-77-4, Superoxide 50812-37-8, Glutathione
 transferase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase
 inhibitors for treatment of degenerative diseases)

IT 42228-92-2, Acivicin 42228-92-2D,
 Acivicin, derivs. 72669-53-5 334700-46-8 334700-46-8D,
 derivs.
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (γ -glutamyl transpeptidase
 inhibitors for treatment of degenerative diseases)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT 9046-27-9, γ -Glutamyl
 transpeptidase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase
 inhibitors for treatment of degenerative diseases)

RN 9046-27-9 HCPLUS

CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L76 ANSWER 2 OF 2 HCPLUS COPYRIGHT 2005 ACS on STN
 AN 2001:699555 HCPLUS

DN 136:4208
 ED Entered STN: 26 Sep 2001
 TI Enhanced gamma-glutamyl transpeptidase
 expression and superoxide production in Mpv17-/- glomerulosclerosis mice
 AU Wagner, Gunter; Stettmaier, Kurt; Bors, Wolf; Sies,
 Helmut; Wagner, Eva-Maria; Reuter, Alexander; Weiher, Hans
 CS Institut fur Physiologische Chemie I, Heinrich-Heine-Universitat,
 Dusseldorf, D-40001, Germany
 SO Biological Chemistry (2001), 382(7), 1019-1025 July.
 CODEN: BICHF3; ISSN: 1431-6730
 PB Walter de Gruyter GmbH & Co. KG
 DT Journal
 LA English
 CC 14-12 (Mammalian Pathological Biochemistry)
 AB Recently, γ -glutamyl transpeptidase, which initiates cleavage of extracellular glutathione, has been shown to promote oxidative damage to cells. Here the authors examined a murine disease model of glomerulosclerosis, involving loss of the Mpv17 gene coding for a peroxisomal protein. In Mpv17-/- cells, enzyme activity and mRNA expression (examined by quant. RT-PCR) of membrane-bound γ -glutamyl transpeptidase were increased, while plasma glutathione peroxidase and superoxide dismutase levels were lowered. Superoxide anion production in these cells was increased as documented by ESR spectroscopy. In the presence of Mn(III)tetrakis(4-benzoic acid)porphyrin, the activities of γ -glutamyl transpeptidase and plasma glutathione peroxidase were unchanged, suggesting a relationship between enzyme expression and the amount of reactive O species. Inhibition of γ -glutamyl transpeptidase by acivicin reverted the lowered plasma glutathione peroxidase and superoxide dismutase activities, indicating reciprocal control of gene expression for these enzymes.
 ST gammaglutamyl transpeptidase superoxide glomerulosclerosis mouse model; glutathione peroxidase reactive oxygen species glomerulosclerosis; superoxide dismutase reactive oxygen species glomerulosclerosis
 IT Gene, animal
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
 IT Gene, animal
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
 IT Kidney, disease
 (glomerulosclerosis; enhanced γ -glutamyl transpeptidase expression and superoxide production in Mpv17-/- glomerulosclerosis mice)
 IT Disease models
 Human
 (γ -glutamyl transpeptidase expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
 IT Transcriptional regulation
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase, glutathione peroxidase, and superoxide dismutase, reciprocal control of gene expression in Mpv17-/- glomerulosclerosis murine model)
 IT Reactive oxygen species
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase, superoxide production, and reactive oxygen species in Mpv17-/- glomerulosclerosis murine model)
 IT 9046-27-9, γ -Glutamyl

transpeptidase 11062-77-4, Superoxide
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase
 expression and superoxide production in Mpv17-/ glomerulosclerosis murine
 model)

IT 9013-66-5, Glutathione peroxidase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase,
 glutathione peroxidase, and superoxide in Mpv17-/ glomerulosclerosis
 murine model)

IT 9054-89-1, Superoxide dismutase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase,
 superoxide dismutase, and superoxide in Mpv17-/ glomerulosclerosis
 murine model)

IT 7782-44-7, Oxygen, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase,
 superoxide production, and reactive oxygen species in
 Mpv17-/ glomerulosclerosis murine model)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT 9046-27-9, γ -Glutamyl
 transpeptidase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (γ -glutamyl transpeptidase
 expression and superoxide production in Mpv17-/ glomerulosclerosis murine
 model)

RN 9046-27-9 HCPLUS
 CN Glutamyltransferase, γ - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d all hitstr 177 tot

L77 ANSWER 1 OF 9 HCPLUS COPYRIGHT 2005 ACS on STN
 AN 2004:202498 HCPLUS
 DN 141:52221
 ED Entered STN: 12 Mar 2004
 TI Increased Oxidative Stress in the Mouse Adriamycin Model of
 Glomerulosclerosis Is Accompanied by Deposition of Ferric Iron and Altered
 GGT Activity in Renal Cortex
 AU Ceyssens, Bart; Pauwels, Marina; Meulemans, Bart; Verbeelen, Dierik; Van
 den Branden, Christiane
 CS Department of Human Anatomy, Vrije Universiteit Brussel and Academic
 Hospital of the Vrije Universiteit Brussel, Brussels, Belg.
 SO Renal Failure (2004), 26(1), 21-27
 CODEN: REFAE8; ISSN: 0886-022X

PB Marcel Dekker, Inc.
 DT Journal
 LA English
 CC 14-12 (Mammalian Pathological Biochemistry)
 AB Chronic renal failure evolves inevitable towards glomerular and tubulo-interstitial sclerosis. This pathol. process involves a disturbed redox status of the kidney tissue, leading to irreversible damage. In this study the authors investigate in an adriamycin model of chronic renal failure in mice the evolution of in vivo hydrogen peroxide production, and the possible role of γ -glutamyl transpeptidase and Fe³⁺ in the process. Histol. changes and Fe³⁺ deposits are evaluated by histochem. staining. To evaluate oxidative stress residual catalase activity, TBARS formation and γ -glutamyl transpeptidase activity are measured spectrophotometrically. While catalase activity remains the same, a decreased residual catalase activity indicates an increased formation of H₂O₂. Both the activity of γ -glutamyl transpeptidase and TBARS formation is increased at early stages of the disease. Fe³⁺ is clearly present in the proximal tubule. Twenty days after adriamycin injection all parameters decrease, probably due to the destruction of the tissue. These data show the involvement of oxidative stress in the progression of adriamycin induced renal failure in mice. Both radical production and oxidative damage are measurable, while the altered activity of γ -glutamyl transpeptidase and the deposition of Fe³⁺ suggest the involvement of these factors in the development of a disturbed redox status in the kidney cortex.
 ST oxidative stress iron glutamyl transpeptidase kidney cortex
 glomerulosclerosis model
 IT Kidney
 (cortex; increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT Kidney, disease
 (failure, chronic; increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT Kidney, disease
 (glomerulosclerosis; increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT Disease models
 Oxidative stress, biological
 (increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT Peroxidation
 (lipid; lipid peroxidn. in increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT Lipids, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (peroxidn.; lipid peroxidn. in increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT 7722-84-1, Hydrogen peroxide, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (H₂O₂ in increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT 9001-05-2, Catalase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (catalase in increased oxidative stress, Fe³⁺ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
 IT 9046-27-9, γ -Glutamyl transpeptidase 20074-52-6, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)

(increased oxidative stress, Fe³⁺ deposition, and altered GGT activity
in renal cortex in glomerulosclerosis in mouse adriamycin model)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT 9046-27-9, γ -Glutamyl

transpeptidase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(increased oxidative stress, Fe³⁺ deposition, and altered GGT activity
in renal cortex in glomerulosclerosis in mouse adriamycin model)

RN 9046-27-9 HCAPLUS

CN Glutamyltransferase, γ - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:491305 HCAPLUS

DN 133:206321

ED Entered STN: 20 Jul 2000

TI Targeted expression of a dominant-negative EGF-R in the kidney reduces
tubulo-interstitial lesions after renal injury

AU Terzi, Fabiola; Burtin, Martine; Hekmati, Mehrak; Federici, Pierre;
Grimber, Giselle; Briand, Pascale; Friedlander, Gerard

CS Institut National de la Sante et de la Recherche Medicale (INSERM) Unite
426 and Department of Physiology, Faculte de Medecine Xavier Bichat,
Universite Paris 7, Paris, 75870, Fr.

SO Journal of Clinical Investigation (2000), 106(2), 225-234
CODEN: JCINAO; ISSN: 0021-9738

PB American Society for Clinical Investigation

DT Journal

LA English

CC 14-12 (Mammalian Pathological Biochemistry)

AB The role of EGF in the evolution of renal lesions after injury is still controversial. To determine whether the EGF expression is beneficial or detrimental, we generated transgenic mice expressing a COOH-terminal-truncated EGF-R under the control of the kidney-specific type 1 γ -glutamyl transpeptidase promoter. As expected, the transgene was expressed exclusively at the basolateral membrane of proximal tubular cells. Under basal conditions, transgenic mice showed normal renal morphol. and function. Infusion of EGF to transgenic animals revealed that the mutant receptor behaved in a dominant-neg. manner and prevented EGF-signaled EGF-R autophosphorylation. We next evaluated the impact of transgene expression on the development of renal lesions in two models of renal injury. After 75% reduction of renal mass, tubular dilations were less severe in transgenic mice than in wild-type animals. After prolonged renal ischemia, tubular atrophy and interstitial fibrosis were reduced in transgenic mice as compared with wild-type mice. The beneficial effect of the transgene included a reduction of tubular-cell proliferation, interstitial collagen accumulation, and mononuclear cell infiltration. In conclusion, functional inactivation of the EGF-R in renal proximal tubular cells reduced tubulo-interstitial lesions after renal injury. These data suggest that blocking the EGF pathway may be a therapeutic strategy to reduce the progression of chronic renal failure.

ST kidney tubulointerstitial injury EGF receptor

IT Phosphorylation, biological
(autophosphorylation; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Kidney, disease
(failure, chronic; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Kidney, disease
(interstitial fibrosis; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Kidney, disease
(ischemia; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Phosphorylation, biological
(receptor; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Epidermal growth factor receptors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Kidney, disease
(tubulointerstitial; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT 62229-50-9, Epidermal growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L77 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2000:414925 HCAPLUS
 DN 133:294841
 ED Entered STN: 22 Jun 2000
 TI Contribution of γ glutamyl transpeptidase to oxidative damage of ischemic rat kidney
 AU Cutrin, Juan C.; Zingaro, Barbara; Camandola, Simonetta; Boveris, Alberto;
 Pompella, Alfonso; Poli, Giuseppe
 CS Department of Clinical and Biological Sciences, University of Turin,
 Turin, Italy
 SO Kidney International (2000), 57(2), 526-533
 CODEN: KDYIA5; ISSN: 0085-2538
 PB Blackwell Science, Inc.
 DT Journal
 LA English
 CC 14-12 (Mammalian Pathological Biochemistry)
 AB Background. A variety of mechanisms have been considered in the pathogenesis of the cell damage occurring in the kidney that is undergoing transient ischemia. However, little information is available about the

role of oxidative stress in building up the tissue injury in the hypoxic organ during short-term ischemia. Methods. After a standard brief period (25 min) of unilateral kidney ischemia in rats, pretreated or not with acivicin ($60 \mu\text{mol/L/kg i.v.}$), tissue samples from both ischemic and non-ischemic kidneys were obtained to measure malondialdehyde (MDA) and glutathione (GSH) content, γ glutamyl transpeptidase (GGT) activity by spectrophotometry, localization and intensity of enzyme activity, and tissue damage by histochem. Results. GGT activity was found to be increased in both cortical and medullar zones of the ischemic kidneys, where the GSH level was only slightly decreased and the MDA level, in contrast, was markedly increased; in parallel, the cytosolic volume of the proximal tubular (PT) cells showed a significant increment. The animal pretreatment with acivicin, a specific inhibitor of GGT, besides preventing the up-regulation of the enzyme during ischemia, afforded good protection against the observed changes of MDA and GSH tissue levels, as well as of tubular cell volume Conclusions. Ex vivo data supporting a net pro-oxidant effect of up-regulated GGT during short-term ischemia of rat kidney have been obtained. The enzyme stimulation appears to contribute to the renal morphol. damage exerted by a brief hypoxic condition at the level of PT cells. The actual impact on kidney function by GGT-dependent oxidative damage during transient ischemia and the potential protective action of GGT inhibitors require subsequent investigation.

- ST glutamyl transpeptidase kidney ischemia oxidative damage
- IT Kidney
 - (cortex; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Cytoplasm
 - (cytosol; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Kidney, disease
 - (ischemia; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Transplant and Transplantation
 - Transplant and Transplantation
 - (kidney; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Peroxidation
 - (lipid; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Kidney
 - (medulla; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Lipids, biological studies
 - RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 - (peroxidn.; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Kidney
 - (proximal tubule; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Kidney
 - Kidney
 - (transplant; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT Oxidative stress, biological
 - (γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT 9046-27-9, γ Glutamyl transpeptidase
 - RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
 - (γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)
- IT 70-18-8, Glutathione, biological studies 542-78-9, Malondialdehyde

RL: BOC (Biological occurrence); BSU (Biological study, unclassified);
 BIOL (Biological study); OCCU (Occurrence)
 (γ glutamyl transpeptidase role in oxidative damage of ischemic
 rat kidney)

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L77 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:668606 HCAPLUS

DN 132:164752

ED Entered STN: 21 Oct 1999

TI Transglutaminase transcription and antigen translocation in experimental renal scarring

AU Johnson, Timothy S.; Skill, N. James; El Nahas, A. Meguid; Oldroyd, Simon D.; Thomas, Graham L.; Douthwaite, Julie A.; Haylor, John L.; Griffin, Martin

CS Northern General Hospital Trust, Sheffield Kidney Institute, Sheffield, NG11 8NS, UK

SO Journal of the American Society of Nephrology (1999), 10(10), 2146-2157

CODEN: JASNEU; ISSN: 1046-6673

PB Lippincott Williams & Wilkins

DT Journal

LA English

CC 14-12 (Mammalian Pathological Biochemistry)

AB It was recently demonstrated that renal tissue transglutaminase (tTg)

protein and its catalytic product the $\epsilon(\gamma\text{-glutamyl})$ lysine protein cross-link are significantly increased in the subtotal (5/6) nephrectomy model (SNx) of renal fibrosis in rats. It was proposed that the enzyme had two important physiol. functions in disease development; one of stabilizing the increased extracellular matrix (ECM) by protein crosslinking, the other in a novel form of tubular cell death. This study, using the same rat SNx model, demonstrates first by Northern blotting that expression of tTg mRNA when compared with controls is increased by day 15 (+70% increase), then rises steadily, peaking at day 90 (+391%), and remains elevated at 120 d (+205%) when compared with controls. In situ hybridization histochem. demonstrated that the tubular cells were the major site of the addnl. tTg synthesis. Immunohistochem. on cryostat sections revealed a sixfold increase in ECM-bound tTg antigen at 90-d post-SNx, whereas in situ transglutaminase activity demonstrated by the incorporation of fluorescein cadaverine into cryostat sections indicated a 750% increase on day 90 in SNx animals. This increased activity was extracellular and predominantly found in the peritubular region. These results indicate that increased tTg gene transcription by tubular cells underlies the major changes in renal tTg protein reported previously in SNx rats, and that the presence of the $\epsilon(\gamma\text{-glutamyl})$ lysine cross-links in the extracellular environment is the result of the extracellular action of tTg. These changes may be in response to tubular cell injury during the scarring process and are likely to contribute to the progressive expansion of the ECM in renal fibrosis.

- ST transglutaminase transcription tubular cell extracellular activity renal scarring
- IT Crosslinking
 (effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)
- IT Collagens, biological studies
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)
- IT Kidney, disease
 (glomerulosclerosis; transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
- IT Kidney, disease
 (interstitial fibrosis; transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
- IT Extracellular matrix
 Transcription, genetic
 (transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
- IT mRNA
 RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PROC (Process)
 (transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
- IT Gene, animal
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
- IT Kidney.
 (tubule; transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
- IT 9001-12-1, Collagenase
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)

IT 17105-15-6, $\epsilon(\gamma\text{-Glutamyl})$ lysine
 RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
 (effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)

IT 80146-85-6, Glutaminylpeptide γ -glutamyltransferase
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
 (transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

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IT 80146-85-6, Glutaminylpeptide γ -

glutamyltransferase

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

RN 80146-85-6 HCPLUS

CN Glutamyltransferase, glutamylpeptide γ - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 5 OF 9 HCPLUS COPYRIGHT 2005 ACS on STN

AN 1999:414377 HCPLUS

DN 131:193953

ED Entered STN: 07 Jul 1999

TI Influence of FR 167653, an inhibitor of TNF- α and IL-1, on the cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats

AU Gardiner, S. M.; Kemp, P. A.; March, J. E.; Bennett, T.

CS School of Biomedical Sciences, Queen's Medical Centre, University of Nottingham Medical School, Nottingham, NG7 2UH, UK

SO Journal of Cardiovascular Pharmacology (1999), 34(1), 64-69

CODEN: JCPCDT; ISSN: 0160-2446

PB Lippincott Williams & Wilkins

DT Journal

LA English

CC 1-8 (Pharmacology)

AB Conscious, male Long Evans rats (350-450 g) chronically instrumented for the measurement of regional hemodynamics, were infused with FR 167653, a dual inhibitor of tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) synthesis (0.32 mg/kg/h) for 24 h, beginning 1 h before coinfusion of saline, or with saline for 24 h beginning 1 h before coinfusion of lipopolysaccharide (150 μ g/kg/h), or with FR 167653 beginning 1 h before coinfusion of lipopolysaccharide. Animals infused with FR 167653 and saline showed progressive hindquarters vasoconstriction over the 24-h period, but this was not different from the change seen in animals ($n = 3$) infused with saline alone. However, plasma anal. at the end of the coinfusion of FR 167653 and saline showed substantial elevation in levels of creatine kinase, lactate dehydrogenase, and potassium, consistent with some tissue damage (heart, liver, or skeletal muscle, or a combination of these). Animals coinjected with saline and lipopolysaccharide showed biphasic decreases in mean arterial blood pressure accompanied by renal hyperemic vasodilatation, and decreases followed by increases in mesenteric and hindquarters flows and vascular conductances. At the end of the infusion period, plasma anal. showed signs of renal dysfunction (elevated creatinine) and hepatic dysfunction (elevated alkaline phosphatase, γ -glutamyl transferase, and alanine aminotransferase). In the presence of FR 167653, the hypotensive effects of lipopolysaccharide were abolished, but regional hemodynamics were unchanged, as were signs of organ dysfunction. One explanation of these observations is that FR 167653 causes a relative improvement in cardiac function during infusion of lipopolysaccharide, and this opposes the hypotensive effects of the latter, in spite of its persistent vasodilator effects.

ST endotoxic shock cardiovascular system FR 167653; organ damage endotoxemia FR 167653; hypotension endotoxemia FR 167653

IT Heart, disease

(cardiomyopathy; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)

IT Cardiovascular system

Hypotension

(effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)

IT Interleukin 1

Tumor necrosis factors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)

- IT Kidney, disease
 Liver, disease
 Muscle, disease
 (injury; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
- IT Vasodilation
 (renal hyperemic; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
- IT Shock (circulatory collapse)
 (septic; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
- IT 158876-66-5, FR 167653
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)

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L77 ANSWER 6 OF 9 HCPLUS COPYRIGHT 2005 ACS on STN

AN 1997:409983 HCPLUS

DN 127:134251

ED Entered STN: 02 Jul 1997

TI The role of transglutaminase in the rat subtotal nephrectomy model of renal fibrosis

AU Johnson, Timothy S.; Griffin, Martin; Thomas, Graham L.; Skill, James; Cox, Ann; Yang, Bin; Nicholas, Ben; Birckbichler, Paul J.; Muchaneta-Kubara, Chiwoneso; El Nahas, A. Meguid

CS Sheffield Kidney Institute, Northern General Hospital NHS Trust, Sheffield, S5 7AU, UK

SO Journal of Clinical Investigation (1997), 99(12), 2950-2960
 CODEN: JCINAO; ISSN: 0021-9738

PB Rockefeller University Press

DT Journal

LA English

CC 14-12 (Mammalian Pathological Biochemistry)

AB Tissue transglutaminase is a calcium-dependent enzyme that catalyzes the crosslinking of polypeptide chains, including those of extracellular matrix (ECM) proteins, through the formation of ϵ -(γ -glutamyl)lysine bonds. This crosslinking leads to the formation of protein polymers that are highly resistant to degradation. As a consequence, the enzyme has been implicated in the deposition of ECM protein in fibrotic diseases such as pulmonary fibrosis and atherosclerosis. In this study, the authors have investigated the involvement of tissue transglutaminase in the development of kidney fibrosis in adult male Wistar rats submitted to subtotal nephrectomy (SNx). Groups of six rats were killed on days 7, 30, 90, and 120 after SNx. As previously described, these rats developed progressive glomerulosclerosis and tubulo-interstitial fibrosis. The tissue level of ϵ -(γ -glutamyl)lysine cross-link (as determined by exhaustive proteolytic digestion followed by cation exchange chromatog.) increased from 3.47 in control to 13.24 nmol/g protein 90 d after SNx. Levels of ϵ -(γ -glutamyl)lysine cross-link correlated well with the renal fibrosis score throughout the 120 observation days ($r = 0.78$). Tissue homogenates showed no significant change in overall transglutaminase activity (¹⁴C putrescine incorporation assay) unless adjusted for the loss of viable tubule cells, when an increase from 5.77 to 13.93 U/mg DNA in cytosolic tissue transglutaminase activity was seen. This increase was supported by Western blot anal., showing a parallel increase in renal tissue transglutaminase content. Immunohistochem. demonstrated that this large increase in ϵ -(γ -glutamyl)lysine cross-link and tissue transglutaminase took place predominantly in the cytoplasm of tubular cells, while immunofluorescence also showed low levels of the ϵ -(γ -glutamyl)lysine cross-link in the extracellular renal interstitial space. The number of cells showing increases in tissue transglutaminase and its cross-link product, ϵ -(γ -glutamyl)lysine, appeared greater than those showing signs of typical apoptosis as determined by *in situ* end-labeling. This observed association between tissue transglutaminase, ϵ -(γ -glutamyl)lysine cross-link, and renal tubulointerstitial scarring in rats submitted to SNx suggests that tissue transglutaminase may play an important role in the development of exptl. renal fibrosis and the associated loss of tubule integrity.

ST transglutaminase subtotal nephrectomy model renal fibrosis

IT Kidney, disease
 (glomerulosclerosis; renal transglutaminase and ϵ -(γ -glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT Kidney, disease
 (interstitial fibrosis; renal transglutaminase and ϵ -(γ -glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT Cytoplasm
 Disease models
 Extracellular matrix
 (renal transglutaminase and ϵ -(γ -glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT 80146-85-6, Glutaminylpeptide γ -glutamyltransferase
 RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 (renal transglutaminase and ϵ -(γ -glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT 17105-15-6, ϵ -(γ -Glutamyl)lysine
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 (renal transglutaminase and ϵ -(γ -glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT 80146-85-6, Glutaminylpeptide γ -glutamyltransferase
 RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological

study); OCCU (Occurrence)
 (renal transglutaminase and ϵ -(γ -glutamyl)lysine in rat
 subtotal nephrectomy model of renal fibrosis)

RN 80146-85-6 HCPLUS
 CN Glutamyltransferase, glutaminylpeptide γ - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 7 OF 9 HCPLUS COPYRIGHT 2005 ACS on STN
 AN 1988:53265 HCPLUS
 DN 108:53265
 ED Entered STN: 20 Feb 1988
 TI Effects of inhibition and modulation of gamma-glutamyltransferase on glutamine and glutamate metabolism in control and acidotic rat proximal tubules
 AU Dass, Proveen D.; Lawson, Lydia R.; Delaney, Vera; Bourke, Edmund
 CS Sch. Med., Emory Univ., Atlanta, GA, USA
 SO Mineral and Electrolyte Metabolism (1987), 13(6), 433-41
 CODEN: MELMDI; ISSN: 0378-0392
 DT Journal
 LA English
 CC 13-2 (Mammalian Biochemistry)
 AB In rat proximal tubules, compds. known to activate γ -glutamyltransferase (γ -GT) including the endogenously produced organic anion hippurate, induced a significant increase in glutamine-ammoniogenesis both in nonacidosis and chronic metabolic acidosis, although in absolute terms the increase was not more marked under the latter conditions. AT-125, which irreversibly inactivates gamma-GT, but not phosphate-dependent glutaminase, reduced the production of NH₃ from glutamine in both acid-base states. In absolute terms, again, this reduction was similar under both acid-base conditions, implying an unimportant role for γ -GT in vitro in the augmentation in renal ammoniogenesis induced by chronic metabolic acidosis. Maleate-stimulated glutamine-ammoniogenesis, recently attributed to its intramitochondrial inhibitory effect in the dog, is substantially due to the activation of γ -GT in rat proximal tubules.
 ST glutamyltransferase gamma kidney regulation; glutamine ammonia metab kidney
 IT Gluconeogenesis
 (from glutamine, maleate and other compds. inhibition of, in kidney proximal tubule)
 IT Acidosis
 (chronic, γ -glutamyltransferase regulation in kidney proximal tubule in relation to)
 IT Kidney, metabolism
 (proximal tubule, glutamate and glutamine metabolism by, γ -glutamyltransferase regulation in, acidosis in relation to)
 IT 7664-41-7, Ammonia, biological studies
 RL: FORM (Formation, nonpreparative)
 (formation of, from glutamine, regulation of, γ -glutamyltransferase regulation in kidney proximal tubule in)
 IT 65-85-0, Benzoic acid, biological studies
 RL: BIOL (Biological study)
 (glutamate and glutamine metabolism by kidney proximal tubule response to, γ -glutamyltransferase in)
 IT 56-86-0, Glutamic acid, biological studies
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (metabolism of, by kidney proximal tubule, γ -glutamyltransferase regulation in)
 IT 56-85-9, Glutamine, biological studies
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (metabolism of, in kidney proximal tubule, γ -glutamyltransferase regulation in)

IT 9046-27-9, γ - Glutamyltransferase
 RL: PROC (Process)
 (of kidney proximal tubule, regulation of, in glutamate and glutamine metabolism regulation, acidosis in relation to)

IT 151-21-3, biological studies
 RL: BIOL (Biological study)
 (γ - glutamyltransferase inactivation by AT-125 in presence of, in kidney proximal tubule, glutamate and glutamine metabolism in response to)

IT 42228-92-2, AT-125
 RL: BIOL (Biological study)
 (γ - glutamyltransferase inactivation by, in kidney proximal tubule, glutamate and glutamine metabolism in response to)

IT 61-78-9, p-Aminohippuric acid 110-16-7, Maleic acid, biological studies
 495-69-2, Hippuric acid 2051-95-8, 3-Benzoylpropionic acid
 RL: BIOL (Biological study)
 (γ - glutamyltransferase stimulation by, in kidney proximal tubule, glutamate and glutamine metabolism response to)

IT 9046-27-9, γ - Glutamyltransferase
 RL: PROC (Process)
 (of kidney proximal tubule, regulation of, in glutamate and glutamine metabolism regulation, acidosis in relation to)

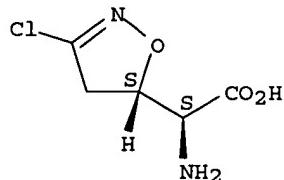
RN 9046-27-9 HCPLUS
 CN Glutamyltransferase, γ - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

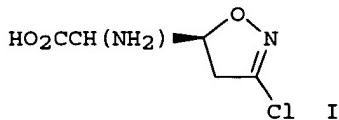
IT 42228-92-2, AT-125
 RL: BIOL (Biological study)
 (γ - glutamyltransferase inactivation by, in kidney proximal tubule, glutamate and glutamine metabolism in response to)

RN 42228-92-2 HCPLUS
 CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 (α S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

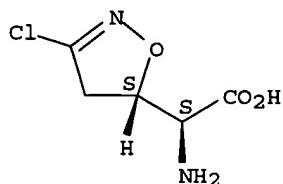


L77 ANSWER 8 OF 9 HCPLUS COPYRIGHT 2005 ACS on STN
 AN 1987:470402 HCPLUS
 DN 107:70402
 ED Entered STN: 05 Sep 1987
 TI Embryotoxicity elicited by inhibition of γ -glutamyltransferase by Acivicin and transferase antibodies in cultured rat embryos
 AU Stark, Kevin L.; Harris, Craig; Juchau, Mont R.
 CS Sch. Med., Univ. Washington, Seattle, WA, 98195, USA
 SO Toxicology and Applied Pharmacology (1987), 89(1), 88-96
 CODEN: TXAPA9; ISSN: 0041-008X
 DT Journal
 LA English
 CC 1-6 (Pharmacology)
 GI



- AB Acivicin (AT-25; I) and IgG isolated from goat anti- γ -glutamyltransferase antiserum were used to inhibit the activity of γ -glutamyl transferase (GGT, EC 2.3.2.2) in rat conceptuses cultured from days 10 to 11 of gestation. Inhibition of GGT by either Acivicin or anti-GGT IgG produced embryotoxicity and malformations, although each compound produced a unique spectrum of effects. Acivicin, at an initial concentration in the culture medium of 5 μ M, produced a marked decrease in yolk sac vasculature and was associated with embryonic malformations such as neural tube necrosis, microophthalmia, and cephalic edema after 24 h exposure. These malformations were accompanied by significant decreases in both embryonic and yolk sac protein, yolk sac GGT activity, as well as embryonic GSH levels. In contrast, anti-GGT IgG produced no apparent effects on yolk sac vasculature or protein after exposure of conceptuses to an initial concentration of 50 μ g IgG/mL culture medium, even though equal inhibition of yolk sac GGT (30%) was achieved by each inhibitor. Exposure to IgG (50 μ g/mL) for 24 h was associated with decreased embryonic protein; decreased levels of GSH in the embryo were observed after both 3 and 24 h. The dichotomy of effects on the yolk sac by the 2 compds. indicates that Acivicin produced these effects by mechanisms other than by GGT inhibition alone. Evidently the inhibition of GGT in rat embryos undergoing organogenesis can elicit embryotoxic effects and produce alterations in GSH levels. The capacity of the anti-GGT antibody to inhibit the GGT activity in the yolk sac (while having no apparent effect on yolk sac morphol.), and yet influence the embryo by decreasing protein and GSH levels, underscores the important role of the yolk sac during the highly sensitive stages of organogenesis.
- ST glutamyltransferase Acivicin embryo; teratogenesis
Acivicin glutamyltransferase
- IT Teratogenesis
(Acivicin and glutamyltransferase antibodies in relation to)
- IT Antibodies
RL: BIOL (Biological study)
(to glutamyltransferase, embryonic growth parameters response to, Acivicin embryo toxicity in relation to)
- IT 42228-92-2, Acivicin
RL: BIOL (Biological study)
(embryo toxicity of, glutamyltransferase inhibition in relation to)
- IT 70-18-8, Glutathione, biological studies
RL: BIOL (Biological study)
(of embryo, Acivicin effect on)
- IT 42228-92-2, Acivicin
RL: BIOL (Biological study)
(embryo toxicity of, glutamyltransferase inhibition in relation to)
- RN 42228-92-2 HCPLUS
CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-, (α S,5S)- (9CI) (CA INDEX NAME)

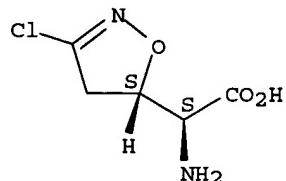
Absolute stereochemistry.



L77 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1982:16560 HCAPLUS
 DN 96:16560
 ED Entered STN: 12 May 1984
 TI Differential effect of AT-125 on rat renal glutaminase activities
 AU Shapiro, Richard A.; Curthoys, Norman P.
 CS Sch. Med., Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
 SO FEBS Letters (1981), 133(1), 131-4
 CODEN: FEBLAL; ISSN: 0014-5793
 DT Journal
 LA English
 CC 7-3 (Enzymes)
 Section cross-reference(s): 13, 14
 AB AT-125, a glutamine antagonist, inhibits the γ -glutamyltranspeptidase (I) and the associated phosphate-independent glutaminase (II) activity of rat kidney brush border membranes without affecting the phosphate-dependent II. This selective inhibition of phosphate-independent II activity by AT-125 enables the determination of the relative contribution of the II activities to glutamine metabolism in crude homogenates and further substantiates that the inhibited activity is due to I, as both glutamine and γ -glutamyl-p-nitroanilide substrate utilization is inhibited. Injection of AT-125 inhibited I activity in vivo but had only a slight effect (.apprx.1.3-fold increase) on NH₃ excretion in rats made acutely acidotic and no effect on increased plasma glutamine or urine acidification associated with acute acidosis. Thus, I is not essential to the adaptive increase in NH₃ synthesis observed with the onset of acidosis.
 ST glutaminase inhibition AT125
 glutamyltranspeptidase kidney; acidosis
 glutamyltranspeptidase glutaminase kidney
 IT Kidney, composition
 (glutamyl transpeptidase and associated glutaminase activity of brush border membrane of, AT-125 selective inhibition of)
 IT Acidosis
 (glutamyltranspeptidase of kidney brush border membrane in relation to)
 IT 42228-92-2
 RL: BIOL (Biological study)
 (glutaminase activity of glutamyltranspeptidase inhibition by, selective glutaminase determination in relation to)
 IT 9046-27-9
 RL: BIOL (Biological study)
 (glutaminase activity of, of kidney brush border membrane, ATP-125 selective inhibition of)
 IT 9001-47-2
 RL: BIOL (Biological study)
 (glutamyltranspeptidase-associated, of kidney brush border membrane, AT-125 selective inhibition of)
 IT 9001-78-9
 RL: BIOL (Biological study)
 (of kidney brush border membrane, in acidosis)
 IT 14798-03-9, biological studies
 RL: BIOL (Biological study)
 (resorption of, by kidney in acidosis, glutamyltranspeptidase in relation to)

IT 42228-92-2
 RL: BIOL (Biological study)
 (glutaminase activity of glutamyltranspeptidase
 inhibition by, selective glutaminase determination in relation to)
 RN 42228-92-2 HCPLUS
 CN 5-Isoazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 (α S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 9046-27-9
 RL: BIOL (Biological study)
 (glutaminase activity of, of kidney brush border membrane, ATP-125
 selective inhibition of)
 RN 9046-27-9 HCPLUS
 CN Glutamyltransferase, γ - (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> b home
 FILE 'HOME' ENTERED AT 15:50:49 ON 21 JUN 2005

=>

=> d his full

(FILE 'HOME' ENTERED AT 07:58:31 ON 22 JUN 2005)

FILE 'REGISTRY' ENTERED AT 07:58:48 ON 22 JUN 2005
ACT HAR325INH/A

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L1  ( 1) SEA ABB=ON PLU=ON US20040115284/PN OR (EP2000-107406# OR
      WO2002-EP1799#/AP, PRN
L2      SEL PLU=ON L1 1- RN :      35 TERMS
L3  ( 35) SEA ABB=ON PLU=ON L2
L4  ( 2) SEA ABB=ON PLU=ON L3 AND GAMMA
L5      1 SEA ABB=ON PLU=ON L4 AND ?TRANSFER?/CNS

      ACT HAR325INHB/A

L6  494 SEA ABB=ON PLU=ON (GAMMA (1A) (GT# OR GLUTAMYLPEPTIDAS? OR
      GLUTAMYLTRANSFERAS? OR GLUTAMYL (1A) (?PEPTIDAS? OR ?TRANSFERAS
      E?)))/CNS
      ACT HAR325C10/A

L7  ( 11) SEA ABB=ON PLU=ON C5H7CLN2O3 AND NOC3/ES
L8      9 SEA ABB=ON PLU=ON L7 NOT (ACETAMIDE OR COMPD OR COMPOUND)

      ACT HAR325F0/A

L9      STR
L10     119 SEA SSS FUL L9
      
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FILE 'HCAPLUS' ENTERED AT 08:00:40 ON 22 JUN 2005
ACT HAR325ACI/Q

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L11    QUE ABB=ON PLU=ON ISOXZOLACET?(1A) ACID (1A)AMINO(1A)CHLORO
      (2A) (DIHYDRO OR DI (1A)HYDRO) OR ACIVICIN# OR AT125 OR
      AT(1A)125 OR NSC163501 OR NSC(1A) (163501 OR 163(1A)501) OR
      U42126 OR U(1A) (42126 OR 42(1A)126)

      ACT HAR325GGT/Q

L12    QUE ABB=ON PLU=ON GLUTAMYLTRANSFERAS? OR GLUTAMYLPEPTIDAS?
      OR GLUTAMYLTRANSPEPTIDAS? OR GGT OR GAMMA (1A) (GT# OR GPT OR
      GLUTAM? (1A) (?PEPTIDAS? OR ?TRANSFERAS?)) OR "EC2.3.2.2" OR
      "E.C.2.3.2.2" OR (EC OR E(1A)C) (1A) "2.3.2.2"
      
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FILE 'MEDLINE' ENTERED AT 08:39:18 ON 22 JUN 2005

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L13    18645 SEA ABB=ON PLU=ON L5 OR L6 OR L12
L15      QUE ABB=ON PLU=ON (C12.777.419. OR GLOMERULONEPHRITIS,
      MEMBRANOUS+NT OR DIABETIC NEUROPATHIES+NT) /CT
L16    25 SEA ABB=ON PLU=ON L14 AND L15
L17    20 SEA ABB=ON PLU=ON L16 AND PY<=2001
      D TRI TOT
L18    8 SEA ABB=ON PLU=ON (L8 OR L10 OR L11) AND L17
      D TRI TOT
      E WEIHER H/AU
L19    35 SEA ABB=ON PLU=ON ("WEIHER H"/AU OR "WEIHER HANS"/AU)
      E SIES H/AU
L20    475 SEA ABB=ON PLU=ON ("SIES H"/AU OR "SIES HELMUT"/AU)
      E WAGNER G/AU
L21    1800 SEA ABB=ON PLU=ON ("WAGNER G"/AU OR "WAGNER G A"/AU OR
      "WAGNER G C"/AU OR "WAGNER G E"/AU OR "WAGNER G F"/AU OR
      "WAGNER G G"/AU OR "WAGNER G GALE"/AU OR "WAGNER G H"/AU OR
      "WAGNER G J"/AU OR "WAGNER G L"/AU OR "WAGNER G LOUIS"/AU OR
      "WAGNER G M"/AU OR "WAGNER G N"/AU OR "WAGNER G P"/AU OR
      "WAGNER G R"/AU OR "WAGNER G S"/AU OR "WAGNER G W"/AU)
      
```

E WAGNER GUNT/AU
L22 26 SEA ABB=ON PLU=ON ("WAGNER GUNTER P"/AU OR "WAGNER GUNTHER
A"/AU)
L23 2 SEA ABB=ON PLU=ON GTX/CS
L24 0 SEA ABB=ON PLU=ON L18 AND (L19 OR L20 OR L21 OR L22 OR L23)
SEL AN L18 1-2 5-8
L25 6 SEA ABB=ON PLU=ON (1998110948/AN OR 2000117960/AN OR
88322348/AN OR 90176799/AN OR 91335465/AN OR 91376832/AN) AND
L18
L26 343 SEA ABB=ON PLU=ON L14 AND (C1. OR C2. OR C3. OR C4. OR C5.
OR C6. OR C7. OR C8. OR C9. OR C10. OR C11. OR C12. OR C13. OR
C14. OR C15. OR C16. OR C17. OR C18. OR C19. OR C20. OR C21.
OR C22. OR C23.)/CT
L27 42 SEA ABB=ON PLU=ON L26 AND (L8 OR L10 OR L11)
L28 35 SEA ABB=ON PLU=ON L27 AND PY<=2001
L29 27 SEA ABB=ON PLU=ON L28 NOT L18
L30 16 SEA ABB=ON PLU=ON (2001146599/AN OR 2002023208/AN OR
2002078526/AN OR 80146834/AN OR 90297270/AN OR 94106631/AN OR
94164747/AN OR 94219988/AN OR 94274542/AN OR 95017052/AN OR
95042327/AN OR 96063893/AN OR 96231934/AN OR 96303179/AN OR
96362741/AN OR 97053363/AN) AND L29
L31 0 SEA ABB=ON PLU=ON L26 AND (L19 OR L20 OR L21 OR L22 OR L23)

FILE 'EMBASE' ENTERED AT 09:23:53 ON 22 JUN 2005

L32 1109 SEA ABB=ON PLU=ON (KIDNEY DISEASE+NT OR C2.610.610.)/CT AND
(L5 OR L6 OR L12)
L33 2020 SEA ABB=ON PLU=ON ISOXAZOLACET?(1A) ACID (1A)AMINO (1A)CHLORO
(2A) (DIHYDRO OR DI (1A)HYDRO) OR ACIVICIN# OR AT125 OR
AT(1A)125 OR NSC163501 OR NSC(1A)(163501 OR 163(1A)501) OR
U42126 OR U(1A)(42126 OR 42(1A)126) OR ACIVIN#
L34 60 SEA ABB=ON PLU=ON (L8 OR L10 OR L33) AND L32
L35 54 SEA ABB=ON PLU=ON L34 AND PY<=2001
E WEIHER H/AU
L36 31 SEA ABB=ON PLU=ON "WEIHER H"/AU
E SIES H/AU
L37 413 SEA ABB=ON PLU=ON ("SIES H"/AU OR "SIES H M"/AU)
E WAGNER G/AU
L38 1487 SEA ABB=ON PLU=ON ("WAGNER G"/AU OR "WAGNER G A"/AU OR
"WAGNER G A L"/AU OR "WAGNER G C"/AU OR "WAGNER G E"/AU OR
"WAGNER G F"/AU OR "WAGNER G G"/AU OR "WAGNER G H"/AU OR
"WAGNER G J"/AU OR "WAGNER G K"/AU OR "WAGNER G L"/AU OR
"WAGNER G M"/AU OR "WAGNER G N"/AU OR "WAGNER G P"/AU OR
"WAGNER G R"/AU OR "WAGNER G S"/AU OR "WAGNER G W"/AU)
E WAGNER GUN/AU
L39 0 SEA ABB=ON PLU=ON GTX/CS
L40 1 SEA ABB=ON PLU=ON L34 AND (L36 OR L37 OR L38)
L41 53 SEA ABB=ON PLU=ON L35 NOT L40
SEL AN L41 1-3 5 8 16 24 31 36 40-42 46 48
L42 14 SEA ABB=ON PLU=ON (1999027532/AN OR 1999194307/AN OR
1999298306/AN OR 2000234081/AN OR 2000416962/AN OR 87211012/AN
OR 88210892/AN OR 90040167/AN OR 90100113/AN OR 90116335/AN OR
91267891/AN OR 93009711/AN OR 94362282/AN OR 96356214/AN) AND
L41
L43 13 SEA ABB=ON PLU=ON (1999027532/AN OR 1999298306/AN OR
2000234081/AN OR 2000416962/AN OR 87211012/AN OR 88210892/AN
OR 90040167/AN OR 90100113/AN OR 90116335/AN OR 91267891/AN OR
93009711/AN OR 94362282/AN OR 96356214/AN) AND L42

=> b medl

FILE 'MEDLINE' ENTERED AT 10:44:49 ON 22 JUN 2005

FILE LAST UPDATED: 21 JUN 2005 (20050621/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP

RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all 125 tot

L25 ANSWER 1 OF 6 MEDLINE on STN
 AN 2000117960 MEDLINE
 DN PubMed ID: 10652029
 TI Contribution of gamma glutamyl transpeptidase to oxidative damage of ischemic rat kidney.
 AU Cutrin J C; Zingaro B; Camandola S; Boveris A; Pompella A; Poli G
 CS Department of Clinical and Biological Sciences, University of Turin, and A.Fa.R.-Fatebenefratelli Hospital, Turin, Italy. juan.cutrin@sluigi.unito.it.
 SO Kidney international, (2000 Feb) 57 (2) 526-33.
 Journal code: 0323470. ISSN: 0085-2538.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200003
 ED Entered STN: 20000320
 Last Updated on STN: 20000320
 Entered Medline: 20000309
 AB BACKGROUND: A variety of mechanisms have been considered in the pathogenesis of the cell damage occurring in the kidney that is undergoing transient ischemia. However, little information is available about the role of oxidative stress in building up the tissue injury in the hypoxic organ during short-term ischemia. METHODS: After a standard brief period (25 min) of unilateral kidney ischemia in rats, pretreated or not with acivicin (60 micromol/L/kg i.v.), tissue samples from both ischemic and non-ischemic kidneys were obtained to measure malondialdehyde (MDA) and glutathione (GSH) content, gamma glutamyl transpeptidase (GGT) activity by spectrophotometry, localization and intensity of enzyme activity, and tissue damage by histochemistry. RESULTS: GGT activity was found to be increased in both cortical and medullar zones of the ischemic kidneys, where the GSH level was only slightly decreased and the MDA level, in contrast, was markedly increased; in parallel, the cytosolic volume of the proximal tubular (PT) cells showed a significant increment. The animal pretreatment with acivicin, a specific inhibitor of GGT, besides preventing the up-regulation of the enzyme during ischemia, afforded good protection against the observed changes of MDA and GSH tissue levels, as well as of tubular cell volume. CONCLUSIONS: Ex vivo data supporting a net pro-oxidant effect of up-regulated GGT during short-term ischemia of rat kidney have been obtained. The enzyme stimulation appears to contribute to the renal morphological damage exerted by a brief hypoxic condition at the level of PT cells. The actual impact on kidney function by GGT-dependent oxidative damage during transient ischemia and the potential protective action of GGT inhibitors require subsequent investigation.
 CT Check Tags: Male
 Animals
 Cell Size
 Cytosol: ME, metabolism
 Enzyme Activation: PH, physiology

Enzyme Inhibitors: PD, pharmacology
 *Ischemia: ME, metabolism
 Isoxazoles: PD, pharmacology
 *Kidney Diseases: EN, enzymology
 Kidney Diseases: ET, etiology
 Kidney Diseases: PA, pathology
 Kidney Tubules: BS, blood supply
 *Kidney Tubules: EN, enzymology
 Kidney Tubules: PA, pathology
 Lipid Peroxidation: PH, physiology
 Microsomes: EN, enzymology
 *Oxidative Stress: PH, physiology
 Rats
 Rats, Wistar
 Renal Circulation
 Research Support, Non-U.S. Gov't
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 *gamma-Glutamyltransferase: ME, metabolism

RN 52583-41-2 (acivicin)
 CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); EC 2.3
 .2.2 (gamma-Glutamyltransferase)

L25 ANSWER 2 OF 6 MEDLINE on STN
 AN 1998110948 MEDLINE
 DN PubMed ID: 9450487
 TI Cytotoxicity and cell-proliferation induced by the nephrocarcinogen hydroquinone and its nephrotoxic metabolite 2,3,5-(tris-glutathion-S-yl)hydroquinone.
 AU Peters M M; Jones T W; Monks T J; Lau S S
 CS Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin, 78712, USA.
 NC ES 07784 (NIEHS)
 GM 39338 (NIGMS)
 SO Carcinogenesis, (1997 Dec) 18 (12) 2393-401.
 Journal code: 8008055. ISSN: 0143-3334.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199802
 ED Entered STN: 19980224
 Last Updated on STN: 19980224
 Entered Medline: 19980211
 AB Hydroquinone, an intermediate used in the chemical industry and a metabolite of benzene, is a nephrocarcinogen in the 2-year National Toxicology Program bioassay in male Fischer 344 rats. Current evidence suggests that certain chemicals may induce carcinogenesis by a mechanism involving cytotoxicity, followed by sustained regenerative hyperplasia and ultimately tumor formation. Glutathione (GSH) conjugates of a variety of hydroquinones are potent nephrotoxicants, and we now report on the effect of hydroquinone and 2,3,5-(tris-glutathion-S-yl)hydroquinone, on site-selective cytotoxicity and cell proliferation in rat kidney. Male Fischer 344 rats (160-200 g) were treated with hydroquinone (1.8 mmol/kg or 4.5 mmol/kg, p.o.) or 2,3,5-(tris-glutathion-S-yl)hydroquinone (7.5 micromol/kg; 1.2-1.5 micromol/rat, i.v.), and blood urea nitrogen (BUN), urinary gamma-glutamyl transpeptidase (gamma-GT), alkaline phosphatase (ALP), glutathione-S-transferase (GST) and glucose were measured as indices of nephrotoxicity. Hydroquinone (1.8 mmol/kg, p.o.) is nephrotoxic in some rats, but not others, but cell proliferation (BrDU incorporation) in proximal tubular cells of the S3M region correlates with the degree of toxicity in individual rats. At 4.5 mmol/kg, hydroquinone causes significant increases in the urinary excretion of gamma-GT, ALP and GST. Pretreatment of rats with acivicin prevents hydroquinone-mediated nephrotoxicity, indicating that toxicity is dependent on the formation of metabolites that require processing by

gamma-GT. Consistent with this view, 2,3,5-(tris-glutathion-S-yl)hydroquinone, a metabolite of hydroquinone, causes increases in BUN, urinary gamma-GT and ALP, all of which are maximal 12 h after administration of 2,3,5-(tris-glutathion-S-yl)hydroquinone. In contrast, the maximal excretion of GST and glucose occurs after 24 h. By 72 h, BUN and glucose concentrations return to control levels, while gamma-GT, ALP and GST remain slightly elevated. Examination of kidney slices by light microscopy revealed the presence of tubular necrosis in the S3M segment of the proximal tubule, extending into the medullary rays. Cell proliferation rates in this region were 2.4, 6.9, 15.3 and 14.3% after 12, 24, 48 and 72 h, respectively, compared to 0.8-2.4% in vehicle controls. Together with the metabolic data, the results indicate a role for hydroquinone-thioether metabolites in hydroquinone toxicity and carcinogenicity.

CT Check Tags: Male

Animals

*Carcinogens: TO, toxicity

Cell Division: DE, drug effects

*Cell Survival: DE, drug effects

*Glutathione: AA, analogs & derivatives

Glutathione: TO, toxicity

*Hydroquinones: TO, toxicity

Isoxazoles: PD, pharmacology

*Kidney: DE, drug effects

Kidney: PA, pathology

Kidney Diseases: CI, chemically induced

Kidney Diseases: PA, pathology

Kidney Neoplasms: CI, chemically induced

Kidney Neoplasms: PA, pathology

Rats

Rats, Inbred F344

Research Support, U.S. Gov't, P.H.S.

gamma-Glutamyltransferase: AI, antagonists & inhibitors

RN 119212-33-8 (2,3,5-(triglutathion-S-yl)hydroquinone); 123-31-9
(hydroquinone); 52583-41-2 (acivicin); 70-18-8 (Glutathione)

CN 0 (Carcinogens); 0 (Hydroquinones); 0 (Isoxazoles); EC 2
.3.2.2 (gamma-Glutamyltransferase)

L25 ANSWER 3 OF 6 MEDLINE on STN

AN 91376832 MEDLINE

DN PubMed ID: 1680251

TI N-(3,5-dichlorophenyl)succinimide nephrotoxicity: evidence against the formation of nephrotoxic glutathione or cysteine conjugates.

AU Rankin G O; Shih H C; Teets V J; Yang D J; Nicoll D W; Brown P I
CS Department of Pharmacology, Marshall University School of Medicine,
Huntington, WV 25755-9310.

NC DK 31210 (NIDDK)

SO Toxicology, (1991) 68 (3) 307-25.

Journal code: 0361055. ISSN: 0300-483X.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199110

ED Entered STN: 19911108

Last Updated on STN: 20000303

Entered Medline: 19911023

AB The agricultural fungicide N-(3,5-dichlorophenyl)succinimide (NDPS) induces nephrotoxicity via one or more metabolites. Previous studies suggested that glutathione is important for mediating NDPS-induced nephropathy. The purpose of this study was to examine the possibility that a glutathione or cysteine conjugate of NDPS or an NDPS metabolite might be the penultimate or ultimate nephrotoxic species. In one set of experiments, male Fischer 344 rats were administered intraperitoneally (i.p.) NDPS (0.4 or 1.0 mmol/kg) 1 h after pretreatment with the gamma glutamyltranspeptidase inhibitor AT-125 (

acivicin) (10 mg/kg, i.p.) and renal function was monitored at 24 and 48 h. In general, AT-125 pretreatment had few effects on NDPS-induced nephropathy. In a second set of experiments, rats were treated i.p. or orally (p.o.) with a putative glutathione (S-(2-(N-(3,5-dichlorophenyl)succinimidyl)glutathione (NDPSG), a cysteine (S-(2-(N-(3,5-dichlorophenyl)succinimidyl)cysteine (NDPSC) (as the methyl ester) or N-acetylcysteine (S-(2-(N-(3,5-dichlorophenyl)succinimidyl)-N-acetylcysteine (NDPSN) conjugate of NDPS (0.2, 0.4 or 1.0 mmol/kg) or vehicle and renal function was monitored at 24 and 48 h. An intramolecular cyclization product of NDPSC, 5-carbomethoxy-2-(N-(3,5-dichlorophenyl)carbamoylmethyl)-1,4-thiazane-3-one (NDCTO) was also examined for nephrotoxic potential. None of the compounds produced toxicologically important changes in renal function or morphology. The in vitro ability of the conjugates to alter organic ion accumulation by cortical slices was also examined. All of the conjugates tested caused a reduction in p-aminohippurate (PAH) accumulation at a conjugate bath concentration of 10(-4) M, but none of the conjugates reduced tetraethylammonium (TEA) uptake. In a third experiment, the ability of the cysteine conjugate beta-lyase inhibitor aminoxyacetic acid (AOAA) (0.5 mmol/kg, i.p.) to alter the nephrotoxicity induced by two NDPS metabolites, N-(3,5-dichlorophenyl)-2-hydroxysuccinimide (NDHS) or N-(3,5-dichlorophenyl)-2-hydroxysuccinamic acid (NDHSA) (0.2 mmol/kg, i.p.), was examined. AOAA pretreatment had no effect on NDHS- or NDHSA-induced nephrotoxicity. These results do not support a role for a glutathione or cysteine conjugate of NDPS or and NDPS metabolite as being the penultimate or ultimate nephrotoxic species.

- CT Check Tags: In Vitro; Male
 Aminoxyacetic Acid: PD, pharmacology
 Animals
 Biotransformation
 *Cysteine: ME, metabolism
 Fungicides, Industrial: ME, metabolism
 *Fungicides, Industrial: TO, toxicity
 *Glutathione: ME, metabolism
 Isoxazoles: PD, pharmacology
 *Kidney Diseases: CI, chemically induced
 Rats
 Rats, Inbred F344
 Research Support, U.S. Gov't, P.H.S.
 *Succinimides: ME, metabolism
 *Succinimides: TO, toxicity
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 24096-53-5 (N-(3,5-dichlorophenyl)succinimide); 52-90-4 (Cysteine);
 52583-41-2 (acivicin); 645-88-5 (Aminoxyacetic Acid); 70-18-8
 (Glutathione)
 CN 0 (Fungicides, Industrial); 0 (Isoxazoles); 0 (Succinimides); EC
 2.3.2.2 (gamma-Glutamyltransferase)
- L25 ANSWER 4 OF 6 MEDLINE on STN
 AN 91335465 MEDLINE
 DN PubMed ID: 1678558
 TI Inhibition of gamma-glutamyl transpeptidase
 potentiates the nephrotoxicity of glutathione-conjugated
 chlorohydroquinones.
 AU Mertens J J; Temmink J H; van Bladeren P J; Jones T W; Lo H H; Lau S S;
 Monks T J
 CS Department of Toxicology, Agricultural University Wageningen, The
 Netherlands.
 NC ES 04662 (NIEHS)
 GM 39338 (NIGMS)
 SO Toxicology and applied pharmacology, (1991 Aug) 110 (1) 45-60.
 Journal code: 0416575. ISSN: 0041-008X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English

FS Priority Journals
 EM 199109
 ED Entered STN: 19911006
 Last Updated on STN: 19950206
 Entered Medline: 19910918
 AB Administration of either 2,5-dichloro-3-(glutathion-S-yl)-1,4-benzoquinone (DC-[GSyl]BQ) or 2,5,6-trichloro-3-(glutathion-S-yl)-1,4-benzoquinone (TC-[GSyl]BQ) to male Sprague-Dawley rats caused dose-dependent (50-200 μ mol/kg; iv) renal proximal tubular necrosis, as evidenced by elevations in blood urea nitrogen (BUN), and in the urinary excretion of lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (gamma-GT) and glucose. Renal proximal tubular necrosis was also confirmed by histological examination of kidney slices prepared from DC-(GSyl)BQ- and TC-(GSyl)BQ-treated animals. Administration of the corresponding hydroquinone conjugates (DC-[GSyl]HQ and TC-[GSyl]HQ), prepared by reducing the quinones with a threefold molar excess of ascorbic acid, resulted in a substantial increase in nephrotoxicity. Moreover, in contrast to other glutathione (GSH)-conjugated hydroquinones, the nephrotoxicity of both DC-(GSyl)HQ and TC-(GSyl)HQ was potentiated when rats were pretreated with AT-125, an irreversible inhibitor of gamma-GT. Neither the quinone-GSH nor the hydroquinone-GSH conjugates caused any effect on liver histology or serum glutamate-pyruvate transaminase levels. The results suggest that coadministration of ascorbic acid with DC-(GSyl)BQ or TC-(GSyl)BQ decreases their interactions with extrarenal nucleophiles, including plasma proteins, and thus increases the concentration of the conjugates delivered to the kidney, and hence toxicity. Furthermore the ability of AT-125 to potentiate the nephrotoxicity of DC-(GSyl)HQ and TC-(GSyl)HQ suggests that metabolism of these conjugates by gamma-GT constitutes a detoxication reaction.
 CT Check Tags: Male
 Animals
 Ascorbic Acid: PD, pharmacology
 *Chloranil: AA, analogs & derivatives
 Chloranil: TO, toxicity
 Chromatography, High Pressure Liquid
 Dose-Response Relationship, Drug
 Drug Synergism
 Electrochemistry
 *Glutathione: AA, analogs & derivatives
 Glutathione: TO, toxicity
 Isoxazoles: PD, pharmacology
 Kidney Cortex: DE, drug effects
 Kidney Cortex: PA, pathology
 *Kidney Diseases: CI, chemically induced
 Kidney Diseases: PA, pathology
 Kidney Tubular Necrosis, Acute: CI, chemically induced
 Oxidation-Reduction
 Rats
 Rats, Inbred Strains
 Research Support, Non-U.S. Gov't
 Research Support, U.S. Gov't, P.H.S.
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 117383-28-5 (2-gluthionyl-3,5,6-trichloro-1,4-benzoquinone); 118-75-2 (Chloranil); 135608-87-6 (2,5-dichloro-3-(glutathionyl-S-yl)-1,4-benzoquinone); 50-81-7 (Ascorbic Acid); 52583-41-2 (acivicin); 70-18-8 (Glutathione)
 CN 0 (Isoxazoles); EC 2.3.2.2
 (gamma-Glutamyltransferase)
 L25 ANSWER 5 OF 6 MEDLINE on STN
 AN 90176799 MEDLINE
 DN PubMed ID: 1689880
 TI Role of gamma-glutamyltranspeptidase and beta-lyase in the nephrotoxicity of hexachloro-1,3-butadiene and methyl mercury in mice.

AU de Ceaurrez J; Ban M
 CS Institut National de Recherche et de Securite, Vandoeuvre, France.
 SO Toxicology letters, (1990 Feb) 50 (2-3) 249-56.
 Journal code: 7709027. ISSN: 0378-4274.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199004
 ED Entered STN: 19900601
 Last Updated on STN: 19960129
 Entered Medline: 19900410
 AB Male Swiss OF1 mice received a single oral dose of either 80 mg/kg hexachloro-1,3-butadiene (HCBD) or 80 mg/kg methyl mercury (MeHg). Examination of cryostat kidney sections stained for alkaline phosphatase (APP) revealed damage to about 50% of the proximal tubules after 8 h. Pretreatment with the gamma-glutamyltranspeptidase (gamma-GT) inactivator AT-125 (Acivin, 50 mg/kg i.p., plus 50 mg/kg p.o., reduced the number of damaged tubules by 59 and 58% in mice treated with HCBD and MeHg, respectively. Pretreatment with the two beta-lyase inhibitors, amino-oxyacetic acid (AOAA, 3 x 100 mg/kg p.o.) and DL-propargylglycine (PPG, 300 mg/kg i.p. plus 300 mg/kg p.o.), reduced HCBD nephrotoxicity by 46 and 59%, respectively, but did not protect against MeHg nephrotoxicity. The results support a role for gamma-GT and beta-lyase in the mouse renal toxicity of HCBD and implicate gamma-GT but not beta-lyase in MeHg-induced nephrotoxicity in mice.
 CT Alkaline Phosphatase: ME, metabolism
 *Alkynes
 Aminooxyacetic Acid: PD, pharmacology
 Animals
 *Butadienes: TO, toxicity
 Glycine: AA, analogs & derivatives
 Glycine: PD, pharmacology
 Isoxazoles: PD, pharmacology
 *Kidney Failure, Acute: CI, chemically induced
 *Kidney Tubular Necrosis, Acute: CI, chemically induced
 Kidney Tubular Necrosis, Acute: EN, enzymology
 Kidney Tubular Necrosis, Acute: PC, prevention & control
 Kidney Tubules, Proximal: DE, drug effects
 Kidney Tubules, Proximal: EN, enzymology
 *Lyases: AI, antagonists & inhibitors
 Lyases: ME, metabolism
 *Methylmercury Compounds: TO, toxicity
 Mice
 Pargyline: AA, analogs & derivatives
 Pargyline: PD, pharmacology
 Staining and Labeling
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 gamma-Glutamyltransferase: ME, metabolism
 RN 52583-41-2 (acivicin); 555-57-7 (Pargyline); 56-40-6 (Glycine);
 64165-64-6 (propargylglycine); 645-88-5 (Aminooxyacetic Acid); 87-68-3
 (hexachlorobutadiene)
 CN 0 (Alkynes); 0 (Butadienes); 0 (Isoxazoles); 0 (Methylmercury Compounds);
 EC 2.3.2.2 (gamma-Glutamyltransferase); EC 3.1.3.1 (Alkaline Phosphatase); EC 4.
 (Lyases)
 L25 ANSWER 6 OF 6 MEDLINE on STN
 AN 88322348 MEDLINE
 DN PubMed ID: 2901150
 TI Effects of AT-125 on the nephrotoxicity of hexachloro-1,3-butadiene in rats.
 AU Davis M E
 CS Department of Pharmacology and Toxicology, West Virginia University,
 Morgantown 26506.

NC S01-R054
 SO Toxicology and applied pharmacology, (1988 Aug) 95 (1) 44-52.
 Journal code: 0416575. ISSN: 0041-008X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 198809
 ED Entered STN: 19900308
 Last Updated on STN: 19950206
 Entered Medline: 19880926
 AB The role of gamma-glutamyl transpeptidase (gamma-GTP) in the nephrotoxicity of hexachloro-1,3-butadiene (HCBD) was studied using male Sprague-Dawley rats pretreated with AT-125 (Acivicin; L-(alpha S, 5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid). Inhibition of gamma-GTP by more than 95% did not affect urine output, glomerular filtration rate, or tubular reabsorption of filtrate, sodium, or glucose. Nephrotoxicity observed during the first 24 hr after HCBD was not decreased by inhibition of gamma-GTP and beyond 24 hr nephrotoxicity was increased, rather than decreased, in the AT-125-pretreated group. HCBD impairs glucose reabsorption and this was greatly increased in the AT-125-pretreated group, indicating that function of the initial segment of the nephron is impaired by HCBD. Since inhibition of gamma-GTP did not protect against HCBD nephrotoxicity, it is concluded that gamma-GTP inhibition does not limit the formation of metabolites(s) which cause HCBD nephrotoxicity. Therefore, distribution of gamma-glutamyltranspeptidase does not account for the selective nephrotoxicity of hexachloro-1,3-butadiene.
 CT Check Tags: Male
 Animals
 *Butadienes: AI, antagonists & inhibitors
 Butadienes: ME, metabolism
 Butadienes: TO, toxicity
 Glycosuria: CI, chemically induced
 Glycosuria: ME, metabolism
 *Isoxazoles: PD, pharmacology
 Kidney Diseases: CI, chemically induced
 *Kidney Diseases: EN, enzymology
 Kidney Function Tests
 *Oxazoles: PD, pharmacology
 Rats
 Rats, Inbred Strains
 Research Support, Non-U.S. Gov't
 Research Support, U.S. Gov't, P.H.S.
 Urine
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 gamma-Glutamyltransferase: ME, metabolism
 RN 52583-41-2 (acivicin); 87-68-3 (hexachlorobutadiene)
 CN 0 (Butadienes); 0 (Isoxazoles); 0 (Oxazoles); EC 2.
 3.2.2 (gamma-Glutamyltransferase)

=> d all 130 tot

L30 ANSWER 1 OF 16 MEDLINE on STN
 AN 2002078526 MEDLINE
 DN PubMed ID: 11805394
 TI Isolated liver perfusion permits administration of high doses of chemotherapeutic agents. Comparison with hepatic artery infusion.
 AU Thorlacius H; Laremark M; Randell M; Hultberg B; Jeppsson B
 CS Department of Surgery, Malmo University Hospital, Malmo, Sweden.
 SO European surgical research. Europaische chirurgische Forschung. Recherches chirurgicales europeennes, (2001 Sep-Dec) 33 (5-6) 342-7.

CY Journal code: 0174752. ISSN: 0014-312X.
 CY Switzerland
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200204
 ED Entered STN: 20020128
 Last Updated on STN: 20020410
 Entered Medline: 20020409
 AB Tumor cells are dependent on glutamine metabolism and acivicin, which is a selective glutamine antagonist, has been shown to effectively retard tumor growth in several malignancies. However, systemic treatment with acivicin is associated with significant side effects. The purpose of the present study was to examine whether use of an in vivo isolated liver perfusion model may allow administration of lethal doses of acivicin and compare it to regional infusion of acivicin in the hepatic artery. Five days after tumor inoculation, acivicin was administered by an isolated liver perfusion model or by regional infusion via the hepatic artery. It was found that regional infusion of acivicin (5 and 10 mg/kg) via the hepatic artery caused systemic illness and diarrhea, and all animals in this group died within 3 days. In contrast, we observed no signs of systemic illness, diarrhea or hepatocellular injury in rats receiving isolated liver perfusion with or without acivicin (10 mg/kg) administration. Noteworthy, we found that isolated perfusion with acivicin reduced the glutamine content in liver tumors by 39% compared to perfusion with control medium. In line with this, it was found that isolated perfusion with acivicin (10 mg/kg) inhibited tumor growth in the liver. Taken together, this study suggests that application of the isolated liver perfusion model avoids the toxic and lethal effects of high doses of chemotherapy, herein acivicin, and may provide a useful approach to treat liver tumors in vivo.
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 CT Check Tags: Comparative Study; Male
 *Adenocarcinoma: DT, drug therapy
 Adenocarcinoma: ME, metabolism
 Adenocarcinoma: PA, pathology
 Animals
 *Antineoplastic Agents: AD, administration & dosage
 Glutamine: ME, metabolism
 Hepatic Artery
 Infusions, Intra-Arterial
 *Isoxazoles: AD, administration & dosage
 Isoxazoles: TU, therapeutic use
 *Liver Circulation
 *Liver Neoplasms, Experimental: DT, drug therapy
 Liver Neoplasms, Experimental: ME, metabolism
 Liver Neoplasms, Experimental: PA, pathology
 *Perfusion, Regional
 Rats
 Rats, Inbred WF
 Research Support, Non-U.S. Gov't
 Treatment Outcome
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 52583-41-2 (acivicin); 56-85-9 (Glutamine)
 CN 0 (Antineoplastic Agents); 0 (Isoxazoles); EC 2.
 3.2.2 (gamma-Glutamyltransferase)
 L30 ANSWER 2 OF 16 MEDLINE on STN
 AN 2002023208 MEDLINE
 DN PubMed ID: 11453733
 TI Serotonergic neurotoxicity of 3,4-(+/-)-methylenedioxymethamphetamine and 3,4-(+/-)-methylendioxymethamphetamine (ecstasy) is potentiated by inhibition of gamma-glutamyl transpeptidase.
 AU Bai F; Jones D C; Lau S S; Monks T J
 CS Center for Cellular and Molecular Toxicology, College of Pharmacy,

University of Texas at Austin, Austin, Texas 78712-1074, USA.
 NC DA 108326 (NIDA)
 SO Chemical research in toxicology, (2001 Jul) 14 (7) 863-70.
 Journal code: 8807448. ISSN: 0893-228X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200112
 ED Entered STN: 20020121
 Last Updated on STN: 20020121
 Entered Medline: 20011204
 AB Reactive metabolites play an important role in 3,4- (+/-)-methyleneedioxyamphetamine (MDA) and 3,4- (+/-)-methyleneoxyamphetamine (MDMA; ecstasy)-mediated serotonergic neurotoxicity, although the specific identity of such metabolites remains unclear. 5-(Glutathion-S-yl)-alpha-methyldopamine (5-GSyl-alpha-MeDA) is a serotonergic neurotoxicant found in the bile of MDA-treated rats. The brain uptake of 5-GSyl-alpha-MeDA is decreased by glutathione (GSH), but sharply increases in animals pretreated with acivicin, an inhibitor of gamma-glutamyl transpeptidase (gamma-GT) suggesting competition between intact 5-GSyl-alpha-MeDA and GSH for the putative GSH transporter. gamma-GT is enriched in blood-brain barrier endothelial cells and is the only enzyme known to cleave the gamma-glutamyl bond of GSH. We now show that pretreatment of rats with acivicin (18 mg/kg, ip) inhibits brain microvessel endothelial gamma-GT activity by 60%, and potentiates MDA- and MDMA-mediated depletions in serotonin (5-HT) and 5-hydroxyindole acidic acid (5-HIAA) concentrations in brain regions enriched in 5-HT nerve terminal axons (striatum, cortex, hippocampus, and hypothalamus). In addition, glial fibrillary acidic protein (GFAP) expression increases in the striatum of acivicin and MDA (10 mg/kg) treated rats, but remains unchanged in animals treated with just MDA (10 mg/kg). Inhibition of endothelial cell gamma-GT at the blood-brain barrier likely enhances the uptake into brain of thioether metabolites of MDA and MDMA, such as 5-(glutathion-S-yl)-alpha-MeDA and 2,5-bis-(glutathion-S-yl)-alpha-MeDA, by increasing the pool of thioether conjugates available for uptake via the intact GSH transporter. The data indicate that thioether metabolites of MDA and MDMA contribute to the serotonergic neurotoxicity observed following peripheral administration of these drugs.
 CT Check Tags: Male
 3,4-Methylenedioxymphetamine: AD, administration & dosage
 3,4-Methylenedioxymphetamine: AI, antagonists & inhibitors
 *3,4-Methylenedioxymphetamine: TO, toxicity
 Administration, Cutaneous
 Animals
 *Brain: DE, drug effects
 Brain: ME, metabolism
 Endothelium: ME, metabolism
 Enzyme Inhibitors: PD, pharmacology
 Humans
 *Isoxazoles: PD, pharmacology
 Models, Molecular
 N-Methyl-3,4-methylenedioxymphetamine: AD, administration & dosage
 N-Methyl-3,4-methylenedioxymphetamine: AI, antagonists & inhibitors
 *N-Methyl-3,4-methylenedioxymphetamine: TO, toxicity
 Neurotoxicity Syndromes
 Neurotransmitters: AN, analysis
 Rats
 Rats, Sprague-Dawley
 Research Support, U.S. Gov't, P.H.S.
 Serotonin: ME, metabolism
 Serotonin Agents: AD, administration & dosage
 *Serotonin Agents: TO, toxicity

*gamma-Glutamyltransferase: AI, antagonists & inhibitors
 gamma-Glutamyltransferase: ME, metabolism

RN 42542-10-9 (N-Methyl-3,4-methylenedioxyamphetamine); 4764-17-4
 (3,4-Methylenedioxyamphetamine); 50-67-9 (Serotonin); 52583-41-2
 (acivicin)

CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); 0 (Neurotransmitters); 0 (Serotonin Agents); EC 2.3.2.2
 (gamma-Glutamyltransferase)

L30 ANSWER 3 OF 16 MEDLINE ON STN

AN 2001146599 MEDLINE

DN PubMed ID: 11194048

TI Biliary glutathione secretion in male single comb white leghorn chickens after inhibition of gamma-glutamyl transpeptidase.

AU Song Z; Bottje W G; Cawthon D; Beers K

CS Department of Poultry Science, University of Arkansas, Fayetteville 72701, USA.

SO Poultry science, (2000 Dec) 79 (12) 1829-32.
 Journal code: 0401150. ISSN: 0032-5791.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200103

ED Entered STN: 20010404
 Last Updated on STN: 20010404
 Entered Medline: 20010315

AB The amount of hepatic export of glutathione into bile and the importance of gamma-glutamyl transpeptidase (gammaGT) activity for catabolizing glutathione in the bile duct, have not been reported previously for domestic fowl. Therefore, the primary objective of this study was to establish baseline values of biliary glutathione, and a secondary objective was to investigate the effect of acivicin (AT-125; a gammaGT inhibitor) on biliary glutathione in the chicken. Cannulae were placed in the carotid artery (to measure blood pressure) and into the left bile duct of anesthetized male Single Comb White Leghorn (SCWL) chickens (n = 5; 17 to 18 wk). The right bile duct was clamped between the liver and gall bladder. Bile samples were collected at 15-min intervals into microcentrifuge tubes (on ice) containing serine borate and iodoacetic acid to prevent glutathione oxidation. After two samples were obtained to establish baseline values, retrograde infusion of AT-125 (30 microLmol/kg BW) was given to inhibit gammaGT activity in the biliary tree. Systemic blood pressure of the birds remained above 100 mm Hg throughout each experiment (90 to 120 min). Bile flow did not change significantly during the experiment and ranged between 0.15+/-0.03 and 0.20+/-0.07 mL/15 min per kg BW. Baseline biliary secretion values of reduced glutathione (GSH), oxidized glutathione (GSSG), and total glutathione (TGSH) were 4.6, 5.9, and 17 nmol/min per kg BW. After AT-125 infusion, biliary GSH levels increased from 15 to 31 nmol/min per kg BW, indicating that considerable gammaGT-mediated catabolism of GSH occurred in the biliary tree of SCWL males. These results indicate that considerable turnover of GSH in the livers of domestic chickens is due to biliary excretion and that substantial recovery of GSH occurs through activity of gammaGT in the biliary tree.

CT Check Tags: Male
 Animals
 *Bile: SE, secretion
 Bile Ducts: PH, physiology
 Body Weight
 *Chickens: PH, physiology
 Constriction
 *Enzyme Inhibitors: PD, pharmacology
 *Glutathione: SE, secretion
 Isoxazoles: PD, pharmacology

Liver: ME, metabolism
 Oxidation-Reduction
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 gamma-Glutamyltransferase: ME, metabolism
 RN 52583-41-2 (acivicin); 70-18-8 (Glutathione)
 CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); EC 2.3
 .2.2 (gamma-Glutamyltransferase)

L30 ANSWER 4 OF 16 MEDLINE on STN
 AN 97053363 MEDLINE
 DN PubMed ID: 8897875
 TI Dynamic aspects of glutathione and nitric oxide metabolism in endotoxemic rats.
 AU Minamiyama Y; Takemura S; Koyama K; Yu H; Miyamoto M; Inoue M
 CS Department of Biochemistry, Osaka City University Medical School, Japan.
 SO American journal of physiology, (1996 Oct) 271 (4 Pt 1) G575-81.
 Journal code: 0370511. ISSN: 0002-9513.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199612
 ED Entered STN: 19970128
 Last Updated on STN: 19970128
 Entered Medline: 19961216

AB Glutathione is one of the most abundant thiols in mammalian tissues and plays important roles in the defense mechanism and detoxification of various metabolites, such as reactive xenobiotics and free radicals. Nitric oxide (NO) readily reacts with thiol compounds, thereby generating chemically stable S-nitrosothiols. Although endotoxin has been known to induce NO synthase in various organs, particularly liver and spleen, and enhances the production of NO, correlation between NO and glutathione metabolism in endotoxemic subjects remains to be elucidated. The present work examines the changes in NO and glutathione metabolism in endotoxemic rats. Administration of lipopolysaccharide (LPS) markedly decreased the glutathione levels in plasma and bile, whereas it decreased the hepatic level only slightly. NG-nitro-L-arginine (L-NNA), a NO synthase inhibitor, inhibited the LPS-induced decrease of glutathione in plasma and bile. Administration of LPS increased the biliary levels of gamma-glutamyl transpeptidase (gamma-GTP) without affecting its thiol levels. Acivicin, a gamma-GTP inhibitor, inhibited the LPS-induced decrease of glutathione in plasma and bile without affecting its hepatic levels. Analysis with the use of L-buthionine sulfoximine revealed that the turnover of hepatic glutathione significantly increased in LPS-treated rats by some L-NNA-inhibitable mechanism. These results suggest that endotoxin might enhance the NO production in the liver and other tissues and significantly modulate the interorgan metabolism of reduced glutathione.

CT Check Tags: Male
 Animals
 *Bile: ME, metabolism
 Buthionine Sulfoximine: PD, pharmacology
 *Endotoxemia: ME, metabolism
 *Endotoxins: PD, pharmacology
 Enzyme Inhibitors: PD, pharmacology
 *Glutathione: ME, metabolism
 Isoxazoles: PD, pharmacology
 *Lipopolysaccharides: PD, pharmacology
 *Liver: ME, metabolism
 *Nitric Oxide: ME, metabolism
 Pancreas: ME, metabolism
 Rats
 Rats, Wistar
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 gamma-Glutamyltransferase: ME, metabolism

RN 10102-43-9 (Nitric Oxide); 5072-26-4 (Buthionine Sulfoximine);
 52583-41-2 (acivicin); 70-18-8 (Glutathione)
 CN 0 (Endotoxins); 0 (Enzyme Inhibitors); 0 (Isoxazoles); 0
 (Lipopolsaccharides); EC 2.3.2.
 2 (gamma-Glutamyltransferase)

L30 ANSWER 5 OF 16 MEDLINE on STN
 AN 96362741 MEDLINE
 DN PubMed ID: 8729948
 TI A phase I study of acivicin in refractory pediatric solid tumors. A Pediatric Oncology Group study.
 AU Baruchel S; Bernstein M; Whitehead V M; Devine S; Bell B; Dubowy R; Grier H; Kretschmar C; Langevin A M; Vietti T
 CS McGill University, Montreal, Canada.
 NC CA-20549 (NCI)
 CA-28383 (NCI)
 CA-33587 (NCI)
 +
 SO Investigational new drugs, (1995) 13 (3) 211-6.
 Journal code: 8309330. ISSN: 0167-6997.
 CY United States
 DT (CLINICAL TRIAL)
 (CLINICAL TRIAL, PHASE I)
 Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199610
 ED Entered STN: 19961106
 Last Updated on STN: 19970203
 Entered Medline: 19961021
 AB Forty-two patients with progressive solid tumors and brain tumors were entered in this Phase I study of the glutamine antagonist acivicin given intravenously over thirty minutes daily for five days. The major toxicities encountered were myelosuppression and central nervous system toxicity (nightmares and somnolence). The maximum tolerated dosage on this schedule was 26 mg/M2 daily for five days. Six patients including three patients with brain tumor had stable disease.
 CT Adolescent
 *Antimetabolites, Antineoplastic: AE, adverse effects
 Antimetabolites, Antineoplastic: TU, therapeutic use
 Child
 Child, Preschool
 Drug Resistance, Neoplasm
 *Enzyme Inhibitors: AE, adverse effects
 Enzyme Inhibitors: TU, therapeutic use
 Humans
 Injections, Intravenous
 *Isoxazoles: AE, adverse effects
 Isoxazoles: TU, therapeutic use
 *Neoplasms: DT, drug therapy
 Research Support, U.S. Gov't, P.H.S.
 Tumor Cells, Cultured: DE, drug effects
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 52583-41-2 (acivicin)
 CN 0 (Antimetabolites, Antineoplastic); 0 (Enzyme Inhibitors); 0
 (Isoxazoles); EC 2.3.2.
 (gamma-Glutamyltransferase)

L30 ANSWER 6 OF 16 MEDLINE on STN
 AN 96303179 MEDLINE
 DN PubMed ID: 8723029
 TI Prevention of diabetes in the spontaneously diabetic BB rat by the glutamine antimetabolite acivicin.
 AU Misra M; Duguid W P; Marliss E B
 CS McGill Nutrition and Food Science Centre, Royal Victoria Hospital, Montreal, QC, Canada.

SO Canadian journal of physiology and pharmacology, (1996 Feb) 74
 (2) 163-72.
 Journal code: 0372712. ISSN: 0008-4212.
 CY Canada
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199704
 ED Entered STN: 19970414
 Last Updated on STN: 19980206
 Entered Medline: 19970403
 AB The autoimmune syndrome of the BB rat is associated with a marked increase in glutamine (Gln) metabolism in immune system cells of both diabetes-prone (BBdp) and diabetic (BBd) rats. To test whether inhibition of Gln metabolism prevents diabetes, 17 BBdp received acivicin (1 mg/kg) and 17 received saline subcutaneously every 2 days from age 48 days until diabetes onset or age 186 days. Twenty-seven non-diabetes-prone (BBn) rats served as controls. Acivicin caused some growth effects and a macrocytic anemia, but no other clinical or biochemical side effects. Only one acivicin-treated BBdp became diabetic (age 158 days), compared with saline-treated rats, of which 10 became diabetic and 2 became glucose intolerant ($p < 0.001$). Insulitis was moderate to severe in 88% of the saline-treated BBdp rats, but minimal in most acivicin-treated BBdp rats. Liver glutamine and glutamate tended to be higher in acivicin- than saline-treated BBdp rats. Acivicin caused no change in the proportions of T or B lymphocytes, NK cells, or macrophage phenotypes in spleen or blood; all BBdp rats were typically lymphopenic. Mitogenic responses of splenocytes in vitro were not affected. The results are consistent with the hypothesis that acivicin, by interfering with Gln metabolism, "targets" activated cells of the immune system and thereby attenuates the process and prevents overt diabetes, without major disturbance of Gln levels or generalized immunosuppression. This prevention is not due to a nutritional-growth retardation effect, as diabetes was prevented in females that showed no such effect.
 CT Check Tags: Comparative Study; Female; Male
 Animals
 Blood Cell Count
 *Diabetes Mellitus, Type 1: PC, prevention & control
 Drug Interactions
 Enzyme Inhibitors: PD, pharmacology
 *Enzyme Inhibitors: TU, therapeutic use
 Glucose Tolerance Test
 Glutamic Acid: ME, metabolism
 *Glutamine: ME, metabolism
 Ionomycin: PD, pharmacology
 Isoxazoles: PD, pharmacology
 *Isoxazoles: TU, therapeutic use
 Lymphocyte Subsets: DE, drug effects
 Rats
 Rats, Inbred BB
 Research Support, Non-U.S. Gov't
 Spleen: CY, cytology
 Spleen: DE, drug effects
 Tetradecanoylphorbol Acetate: PD, pharmacology
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 16561-29-8 (Tetradecanoylphorbol Acetate); 52583-41-2 (acivicin)
 ; 56-85-9 (Glutamine); 56-86-0 (Glutamic Acid); 56092-81-0 (Ionomycin)
 CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); EC 2.3
 .2.2 (gamma-Glutamyltransferase)
 L30 ANSWER 7 OF 16 MEDLINE on STN
 AN 96231934 MEDLINE
 DN PubMed ID: 8632493
 TI gamma-Glutamyl transpeptidase mediation of tumor glutathione utilization in vivo.

AU Hochwald S N; Harrison L E; Rose D M; Anderson M; Burt M E
 CS Department of Surgery, Surgical Metabolism Laboratory, Memorial
 Sloan-Kettering Cancer Center, New York, NY 10021, USA.
 SO Journal of the National Cancer Institute, (1996 Feb 21) 88 (3-4)
 193-7.
 Journal code: 7503089. ISSN: 0027-8874.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199607
 ED Entered STN: 19960715
 Last Updated on STN: 20000303
 Entered Medline: 19960702
 AB BACKGROUND: Glutathione is a tripeptide used by cells to protect against oxidative and free radical damage. It may also be involved in biochemical mechanisms that cause some tumors to become resistant to anticancer drugs. gamma-Glutamyl transpeptidase (GGTP) is a membrane-bound enzyme that cleaves extracellular glutathione, providing cells with amino acids necessary for intracellular synthesis of this compound. Increased expression of GGTP has been found in a number of human tumors; however, few studies have examined the contribution of GGTP to tumor glutathione metabolism in vivo. PURPOSE: Our goals were to study the utilization of host glutathione by 3-methylcholanthrene (MCA)-induced sarcomas grown in rats and to evaluate the involvement of tumor GGTP in this process. METHODS: The left ovaries of 21 female Fischer 344 rats were isolated by laparotomy and placed in subcutaneous positions through stab wounds in the abdominal wall. A 3-mm cube of MCA sarcoma was then sutured to each of the isolated ovaries. The MCA implants obliterated the ovarian tissue, yielding isolated tumors with one arterial supply (the ovarian artery) and one draining vein (the ovarian vein, referred to as the tumor vein). After 2 weeks of tumor growth, blood was drawn from the tumor vein, the inferior vena cava (IVC), and the aorta of 16 animals. Glutathione and cysteine concentrations in plasma samples from this blood were determined by high-performance liquid chromatography and used to calculate glutathione and cysteine utilization ratios for the tumor and the systemic circulations $\{[(\text{concentration aorta}-\text{concentration tumor vein})/\text{concentration aorta}] \times 100$ and $\{[(\text{concentration aorta}-\text{concentration IVC})/\text{concentration aorta}] \times 100$, respectively). The utilization ratios from these control animals were compared with those from acivicin (AT-125; an irreversible GGTP inhibitor)-treated rats (the remaining five animals). Data are presented as mean +/- standard deviation; reported P values are from two-tailed tests of statistical significance. RESULTS: In the control animals, glutathione and cysteine concentrations were significantly lower in the tumor vein (3.55 +/- 1.9 and 5.69 +/- 2.8 microM, respectively) and in the IVC (5.65 +/- 2.3 and 7.17 +/- 2.4 microM, respectively) than in the artery (12.48 +/- 5.7 and 12.33 +/- 5.9 microM, respectively; all P values < .05). In addition, the glutathione utilization ratio was significantly higher for the tumor circulation than for the systemic circulation (69% +/- 14% versus 52% +/- 14%; P < .003). The combined glutathione and cysteine utilization ratio was also significantly higher for the tumor circulation than for the systemic circulation (116% +/- 35% versus 88% +/- 28%; P < .02). Treatment with AT-125 lowered the tumor glutathione utilization ratio significantly (45% +/- 12% for treated animals versus 69% +/- 14% for control animals; P < .005). CONCLUSIONS: Our results show that glutathione and cysteine in the host circulation are used by MCA sarcomas. The significant reduction in tumor utilization of serum glutathione after treatment with AT-125, a GGTP inhibitor, indicates that GGTP is important in tumor glutathione metabolism.
 CT Check Tags: Female
 Animals
 Cysteine: ME, metabolism
 Enzyme Inhibitors: PD, pharmacology
 *Glutathione: ME, metabolism

Isoxazoles: PD, pharmacology
 Methylcholanthrene
 Rats
 Rats, Inbred F344
 Sarcoma, Experimental: EN, enzymology
 *Sarcoma, Experimental: ME, metabolism
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 *gamma-Glutamyltransferase: ME, metabolism

RN 52-90-4 (Cysteine); 52583-41-2 (acivicin); 56-49-5
 (Methylcholanthrene); 70-18-8 (Glutathione)

CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); EC 2.3
 .2.2 (gamma-Glutamyltransferase)

L30 ANSWER 8 OF 16 MEDLINE on STN

AN 96063893 MEDLINE

DN PubMed ID: 8519693

TI Inhibition of gamma-glutamyl transpeptidase
 activity at the surface of human myeloid cells is correlated with
 macrophage maturation and transforming growth factor beta production.

AU Bauvois B; Laouar A; Rouillard D; Wietzerbin J

CS Unite 365 INSERM-Institut Curie, Paris, France.

SO Cell growth & differentiation : molecular biology journal of the American
 Association for Cancer Research, (1995 Sep) 6 (9) 1163-70.
 Journal code: 9100024. ISSN: 1044-9523.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199601

ED Entered STN: 19960219
 Last Updated on STN: 19970203
 Entered Medline: 19960125

AB The protease gamma-glutamyl transpeptidase (gamma-GT) activity was detected at the surface of human blood granulocytes and monocytes and myeloblastic HL-60 and monoblastic U937 leukemia cell lines using an enzymatic assay (cleavage of gamma-glu-p-nitroanilide and inhibition by the specific irreversible inhibitor of gamma-GT, i.e., acivicin). Flow cytometric analysis of gamma-GT expression and detection of a 2.4-kb gamma-GT mRNA species by Northern blot analysis confirmed the presence of gamma-GT in cells of the monocytic-granulocytic lineage. Differentiation of HL-60, U937 cells, and blood monocytes along the macrophage pathway or granulocytic maturation of HL-60 cells was accompanied by an increase in gamma-GT mRNA levels without modulation of cell surface gamma-GT activity and protein. When added to leukemic cell cultures, acivicin produced a dose- and time-dependent inhibitory growth effect associated with the induction of morphological features characteristic of macrophage maturation and enhanced surface expression of phenotypic markers CD11b and CD71 characteristic of monocyte development. When cultured in the presence of acivicin, freshly isolated monocytes also underwent characteristic changes in morphology and antigenic phenotype (increase in CD71 and HLA-DR class II) consistent with their differentiation into macrophages. In parallel, a marked production of latent transforming growth factor (TGF)-beta was observed in supernatants of cells cultured with acivicin, although TGF-beta 1 mRNA species were expressed in these cells at a level almost similar to that in unstimulated cell cultures. Moreover, acivicin-treated cells still differentiated into macrophages in the presence of a neutralizing antibody to TGF-beta 1/beta 2. (ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Comparative Study
 Cell Aging: PH, physiology
 Cell Differentiation: PH, physiology
 Cell Membrane: EN, enzymology
 Cells, Cultured

Humans

*Leukemia, Monocytic, Acute: EN, enzymology
 Leukemia, Monocytic, Acute: PA, pathology
 *Leukemia, Myeloid: EN, enzymology
 Leukemia, Myeloid: PA, pathology
 *Macrophages: CY, cytology
 Research Support, Non-U.S. Gov't
 *Transforming Growth Factor beta: BI, biosynthesis
 Tumor Cells, Cultured
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 CN 0 (Transforming Growth Factor beta); EC 2.3.
 2.2 (gamma-Glutamyltransferase)

L30 ANSWER 9 OF 16 MEDLINE on STN

AN 95042327 MEDLINE

DN PubMed ID: 7954424

TI Inhibition of gamma-glutamyl transpeptidase activity by acivicin in vivo protects the kidney from cisplatin-induced toxicity.

AU Hanigan M H; Gallagher B C; Taylor P T Jr; Large M K

CS Department of Cell Biology, University of Virginia Health Sciences Center, Charlottesville 22908.

NC CA 57530 (NCI)

P30-HD28934 (NICHHD)

SO Cancer research, (1994 Nov 15) 54 (22) 5925-9.
 Journal code: 2984705R. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199412

ED Entered STN: 19950110

Last Updated on STN: 19950110

Entered Medline: 19941202

AB Cisplatin [cis-dichlorodiammineplatinum(II)] is a widely used chemotherapeutic drug that is toxic to the proximal tubule cells of the kidney. gamma-Glutamyl transpeptidase (GGT) is localized to the luminal surface of the renal proximal tubules. GGT catalyzes the initial step in the metabolism of glutathione-conjugated drugs to mercapturic acids, some of which are severely nephrotoxic. We proposed that the nephrotoxicity of cisplatin was dependent on the cleavage of a cisplatin-glutathione conjugate by GGT. To test this hypothesis, renal GGT activity was blocked in male Sprague-Dawley rats by acivicin, a non-competitive inhibitor of GGT. Treatment with cisplatin alone caused extensive acute necrosis of the proximal tubules, but the proximal tubule cells appeared normal in rats treated with acivicin prior to cisplatin. Blood urea nitrogen and serum creatinine levels confirmed the protective effect of acivicin. Glutathione is a physiological substrate for GGT. Administration of an 83-fold excess of glutathione 30 min prior to cisplatin also inhibited cisplatin-induced nephrotoxicity. These data provide important new evidence that a large bolus of glutathione blocks the nephrotoxicity of cisplatin by competitively inhibiting GGT. These results indicate that cisplatin is conjugated to glutathione in vivo. The platinum-glutathione conjugate is nontoxic until metabolized by the proximal tubule cells. Formation of the nephrotoxic derivative of cisplatin requires GGT activity.

CT Check Tags: Male

Animals

Blood Urea Nitrogen

Body Weight: DE, drug effects

Cisplatin: AE, adverse effects

*Cisplatin: AI, antagonists & inhibitors

Cisplatin: ME, metabolism

Creatinine: BL, blood

Eating
 Glutathione: ME, metabolism
 *Isoxazoles: PD, pharmacology
 *Kidney: DE, drug effects
 Kidney: EN, enzymology
 Kidney: PA, pathology
 Kidney Tubules, Proximal: DE, drug effects
 Rats
 Rats, Sprague-Dawley

Research Support, U.S. Gov't, P.H.S.
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors

RN 15663-27-1 (Cisplatin); 52583-41-2 (acivicin); 60-27-5
 (Creatinine); 70-18-8 (Glutathione)

CN 0 (Isoxazoles); EC 2.3.2.2
 (gamma-Glutamyltransferase)

L30 ANSWER 10 OF 16 MEDLINE on STN
 AN 95017052 MEDLINE

DN PubMed ID: 7931622

TI Enzymatic barrier protects brain capillaries from leukotriene C4.

AU Black K L; Baba T; Pardridge W M

CS Brain Research Institute, University of California, Los Angeles Medical Center.

NC 1P01NS25554 (NINDS)

1R01NS32103

SO Journal of neurosurgery, (1994 Nov) 81 (5) 745-51.

Journal code: 0253357. ISSN: 0022-3085.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199411

ED Entered STN: 19941222

Last Updated on STN: 20000303

Entered Medline: 19941114

AB Leukotriene C4 (LTC4) increases vascular permeability in systemic, brain tumor, and ischemic brain capillaries, but not in normal brain capillaries. This study examines whether the abundance of gamma-glutamyl transpeptidase (gamma-GTP) in normal brain capillaries might act as an enzymatic barrier to vasoactive leukotrienes in the brain. Blood-brain barrier (BBB) permeability was determined by quantitative autoradiography using ¹⁴C-aminoisobutyric acid. Ischemia was produced by occluding the middle cerebral artery. Seventy-two hours after occlusion, gamma-GTP activity in ischemic brain disappeared, and LTC4 (4-micrograms total dose), which was infused into the carotid artery ipsilateral to the occlusion, selectively increased permeability, Ki, approximately twofold within core ischemic tissue and adjacent tissue, compared to vehicle alone in seven brains (15.53 +/- 6.03 vs. 7.29 +/- 3.36, p < 0.05, and 8.76 +/- 4.02 vs. 4.32 +/- 2.65, p < 0.05, respectively). No effect on BBB was seen in nonischemic brain tissue. Twenty-four hours postocclusion, gamma-GTP activity was still present, and LTC4 infusion did not increase permeability within ischemic tissue. However, inhibition of gamma-GTP with acivicin allowed LTC4 to increase permeability even 24 hours after occlusion in ischemic core and adjacent tissue compared to vehicle alone in seven brains (17.21 +/- 16.32 vs. 8.23 +/- 6.58, p < 0.05, and 11.78 +/- 7.96 vs. 4.56 +/- 1.93, p < 0.01, respectively). Acivicin almost completely blocked both the histochemical activity of gamma-GTP in brain capillaries and the metabolism of LTC4 in isolated bovine capillaries. These findings suggest that gamma-GTP may help normal brain capillaries resist the vasoactive effects of LTC4. In contrast, gamma-GTP is lost in injured brain capillaries, which allows LTC4 (in combination with other factors) to increase vascular permeability in ischemic brain and brain tumors.

CT Check Tags: Female

Animals

Antimetabolites: PD, pharmacology

Autoradiography

Blood-Brain Barrier: DE, drug effects

*Brain: BS, blood supply

Brain: EN, enzymology

Brain Ischemia: EN, enzymology

Brain Ischemia: PA, pathology

Brain Ischemia: PP, physiopathology

Capillaries: DE, drug effects

Capillaries: EN, enzymology

Capillary Permeability: DE, drug effects

Cattle

Isoxazoles: PD, pharmacology

Leukotriene C4: AI, antagonists & inhibitors

Leukotriene C4: ME, metabolism

*Leukotriene C4: PD, pharmacology

Rats

Rats, Wistar

Receptors, Leukotriene: DE, drug effects

Receptors, Leukotriene: ME, metabolism

Research Support, U.S. Gov't, P.H.S.

Time Factors

gamma-Glutamyltransferase: AI, antagonists & inhibitors

*gamma-Glutamyltransferase: PH, physiology

RN 52583-41-2 (acivicin); 72025-60-6 (Leukotriene C4)

CN 0 (Antimetabolites); 0 (Isoxazoles); 0 (Receptors, Leukotriene); 0
(leukotriene C4 receptor); EC 2.3.2
.2 (gamma-Glutamyltransferase)

L30 ANSWER 11 OF 16 MEDLINE on STN

AN 94274542 MEDLINE

DN PubMed ID: 7911799

TI Elimination of glutathione-induced protection from hyperbaric hyperoxia by acivicin.

AU Peacock M D; Schenk D A; Lawrence R A; Morgan J A; Jenkinson S G

CS Lung Metabolic Unit, University of Texas Health Science Center at San Antonio.

SO Journal of applied physiology (Bethesda, Md. : 1985), (1994 Mar)

76 (3) 1279-84.

Journal code: 8502536. ISSN: 8750-7587.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Space Life Sciences

EM 199407

ED Entered STN: 19940729

Last Updated on STN: 19950206

Entered Medline: 19940715

AB Glutathione (GSH) administered intraperitoneally significantly prolongs the time to initial seizure and survival time of rats exposed to hyperbaric hyperoxia (HBO). Acivicin is an antitumor antibiotic that is an inhibitor of gamma-glutamyl transpeptidase (GGT), an enzyme necessary for the breakdown and transport across cell membranes of GSH. To determine whether acivicin treatment alters GSH-induced protection from HBO, rats were dosed with 25 mg/kg of acivicin or vehicle 1 h before O₂ exposure at an inspired O₂ fraction of 1.0 at 4 ATA. Immediately before exposure, rats received GSH (1 mmol/kg) or vehicle. Time to seizure and time to death were recorded during exposure by direct observation. In separate groups of rats on the same dosing schedule, plasma GSH, renal GGT, and brain GGT were measured 15 min after the GSH injection without HBO exposure and 100 min after the beginning of HBO exposure. Renal GGT was decreased to 2.5% of control and brain GGT to 37% of control in the acivicin -dosed rats. Plasma GSH increased 3-fold in rats given acivicin

alone, 52-fold in rats given GSH alone, and 84-fold in rats receiving both acivicin and GSH. Rats dosed with GSH alone had significantly prolonged times to seizure and death compared with all other groups. Rats dosed with GSH after receiving acivicin were not protected from HBO despite the large increase in plasma GSH that occurred in these animals. GSH treatment did not increase tissue GSH in lung, liver, or brain at 160 or 200 min of exposure. (ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Male

Animals

Brain: EN, enzymology

Brain Chemistry: DE, drug effects

*Glutathione: AI, antagonists & inhibitors

Glutathione: ME, metabolism

Glutathione: PD, pharmacology

*Hyperbaric Oxygenation: AE, adverse effects

*Isoxazoles: PD, pharmacology

Kidney: EN, enzymology

Kidney: ME, metabolism

Lung: EN, enzymology

Lung: ME, metabolism

*Oxygen: AI, antagonists & inhibitors

Oxygen: TO, toxicity

Rats

Rats, Sprague-Dawley

Research Support, U.S. Gov't, Non-P.H.S.

Seizures: CI, chemically induced

Seizures: PC, prevention & control

gamma-Glutamyltransferase: AI, antagonists & inhibitors

gamma-Glutamyltransferase: ME, metabolism

RN 52583-41-2 (acivicin); 70-18-8 (Glutathione); 7782-44-7 (Oxygen)

CN 0 (Isoxazoles); EC 2.3.2.2

(gamma-Glutamyltransferase)

L30 ANSWER 12 OF 16 MEDLINE on STN

AN 94219988 MEDLINE

DN PubMed ID: 7909430

TI Nephrotoxicity of 4-amino-3-S-glutathionylphenol and its modulation by metabolism or transport inhibitors.

AU Fowler L M; Foster J R; Lock E A

CS Zeneca Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

SO Archives of toxicology, (1994) 68 (1) 15-23.

Journal code: 0417615. ISSN: 0340-5761.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199405

ED Entered STN: 19940606

Last Updated on STN: 19960129

Entered Medline: 19940524

AB The nephrotoxicity of 4-amino-3-S-glutathionylphenol (PAP-GSH), a known metabolite of 4-amino-phenol (PAP), was determined in male Fischer 344 rats. Administration of a single dose of 40 or 60 mumol kg⁻¹ caused a marked elevation in blood urea nitrogen and an increase in the urinary excretion of glucose, protein and gamma-glutamyltransferase (GGT). These changes were associated with histological alterations in the proximal tubule, where at the lower dose the lesion was restricted to the S3 region of the proximal tubule in the medullary rays, while at the higher dose the lesion extended to affect the S3 region in both the medullary rays and the outer stripe of the outer medulla. Studies with [³⁵S]-PAP-GSH at 40 mumol kg⁻¹ showed selective retention of radioactivity in the kidney, relative to other organs 24 h after dosing and that some radioactivity was covalently bound to renal proteins. Pretreatment of animals with probenecid, an inhibitor of renal organic anion transport, or aminoxyacetic acid, an inhibitor of cysteine conjugate beta-lyase, had little or no effect on the toxicity. In contrast, pretreatment of animals

with acivicin, an inhibitor of gamma-glutamyltransferase, or co-administration of PAP-GSH with ascorbic acid almost completely protected against the nephrotoxicity. This protection was associated with a decreased concentration of radioactivity from [35S]-PAP-GSH in the kidneys and a decrease in the amount covalently bound to renal protein. Thus, the nephrotoxicity of PAP-GSH may be mediated by oxidation and further processing of the glutathione conjugate via gamma-glutamyltransferase.

CT Check Tags: Male
 Aminoxyacetic Acid: PD, pharmacology
 Animals
 Ascorbic Acid: PD, pharmacology
 Blood Urea Nitrogen
 *Glutathione: AA, analogs & derivatives
 Glutathione: ME, metabolism
 Glutathione: PK, pharmacokinetics
 Glutathione: TO, toxicity
 Glycosuria: CI, chemically induced
 Ion Transport
 Isoxazoles: PD, pharmacology
 *Kidney: DE, drug effects
 Kidney: PA, pathology
 Lyases: ME, metabolism
 Oxidation-Reduction
 Phenols: ME, metabolism
 Phenols: PK, pharmacokinetics
 *Phenols: TO, toxicity
 Probenecid: PD, pharmacology
 Proteinuria: CI, chemically induced
 Rats
 Rats, Inbred F344
 Sulfur Radioisotopes: DU, diagnostic use
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 *gamma-Glutamyltransferase: ME, metabolism
 gamma-Glutamyltransferase: UR, urine
 RN 129762-74-9 (4-amino-3-S-glutathionylphenol); 50-81-7 (Ascorbic Acid);
 52583-41-2 (acivicin); 57-66-9 (Probenecid); 645-88-5
 (Aminoxyacetic Acid); 70-18-8 (Glutathione)
 CN 0 (Isoxazoles); 0 (Phenols); 0 (Sulfur Radioisotopes); EC
 2.3.2.2 (gamma-Glutamyltransferase); EC 4. (Lyases)

L30 ANSWER 13 OF 16 MEDLINE on STN
 AN 94164747 MEDLINE
 DN PubMed ID: 7907080
 TI Gamma-glutamyltranspeptidase expression regulates the growth-inhibitory activity of the anti-tumor prodrug gamma-L-glutamyl-4-hydroxy-3-iodobenzene.
 AU Prezioso J A; Hughey R P; Wang N; Damodaran K M; Bloomer W D
 CS Department of Radiation Oncology, University of Pittsburgh School of Medicine, PA 15213.
 NC DK26012 (NIDDK)
 SO International journal of cancer. Journal international du cancer, (1994 Mar 15) 56 (6) 874-9.
 Journal code: 0042124. ISSN: 0020-7136.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199404
 ED Entered STN: 19940412
 Last Updated on STN: 19980206
 Entered Medline: 19940407
 AB gamma-L-glutamyl-4-hydroxy-3-iodobenzene (I-GHB), a novel iodinated analog of gamma-L-glutamyl-4-hydroxybenzene (GHB), demonstrates greater anti-tumor activity in human and in murine melanoma cell lines. These

phenolic amides are substrates for gamma-glutamyltranspeptidase (GGTP; E.C. 2.3.2. 2), a cell-membrane-associated ecto-enzyme which is elevated in a number of tumor systems. We now present data to show that the growth-inhibitory activity of I-GHB and GHB may be mediated via GGTP-catalyzed reactions. The growth-inhibitory activity of I-GHB and GHB in pigmented B16-BL6 melanoma cells was blocked significantly by rabbit anti-rat GGTP polyclonal antibodies. The combination of L-serine and sodium borate, a specific transition-state inhibitor of GGTP, as well as acivicin, a glutamine antagonist and irreversible GGTP inhibitor, inhibited the killing of BL6 cells by GHB and I-GHB. To further define the role of GGTP expression in the regulation of phenolic amide cytotoxicity, GGTP-negative Chinese hamster ovary cells (CHO-K1) were transfected with a functional rat renal cDNA representing the full-length GGTP transcript. I-GHB and GHB were significantly more cytotoxic in GGTP cDNA transfected Chinese hamster ovary (CHO-K1-GGTP) cells than in non-transfected CHO-K1 cells. The combination of L-serine and sodium borate blocked the cytotoxic activity of these pro-drugs and also inhibited GGTP-catalyzed formation of polymerized products from these phenolic amides in intact BL6 melanoma and CHO-K1-GGTP cells. Furthermore, melanin formation from GHB was not observed in non-transfected CHO-K1 cells lacking GGTP expression. The combined data strongly suggest that GGTP-catalyzed hydrolysis of the anti-tumor pro-drugs I-GHB and GHB to 4-aminophenols mediates the expression of antitumor activity.

CT

Animals

Antineoplastic Agents: AI, antagonists & inhibitors

*Antineoplastic Agents: ME, metabolism
Antineoplastic Agents: PD, pharmacology

Borates: PD, pharmacology

CHO Cells: DE, drug effects

*CHO Cells: ME, metabolism

CHO Cells: PA, pathology

Cell Division

*Glutamine: AA, analogs & derivatives

Glutamine: AI, antagonists & inhibitors

Glutamine: ME, metabolism

Glutamine: PD, pharmacology

Glutathione: ME, metabolism

Hamsters

Hydrolysis

Isoxazoles: PD, pharmacology

Melanins: BI, biosynthesis

*Melanoma, Experimental: ME, metabolism

Melanoma, Experimental: PA, pathology

Mice

Phenols: AI, antagonists & inhibitors

*Phenols: ME, metabolism

Phenols: PD, pharmacology

*Prodrugs: ME, metabolism

Prodrugs: PD, pharmacology

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Serine: PD, pharmacology

Transfection

gamma-Glutamyltransferase: AI, antagonists & inhibitors

gamma-Glutamyltransferase: GE, genetics

*gamma-Glutamyltransferase: ME, metabolism

RN 1330-43-4 (sodium borate); 147139-63-7 (gamma-glutamyl-4-hydroxy-3-iodobenzene); 52583-41-2 (acivicin); 56-45-1 (Serine); 56-85-9 (Glutamine); 70-18-8 (Glutathione)

CN 0 (Antineoplastic Agents); 0 (Borates); 0 (Isoxazoles); 0 (Melanins); 0 (Phenols); 0 (Prodrugs); EC 2.3.2.
2 (gamma-Glutamyltransferase)

L30 ANSWER 14 OF 16 MEDLINE on STN

AN 94106631 MEDLINE
 DN PubMed ID: 7904127
 TI Bidirectional membrane transport of intact glutathione in Hep G2 cells.
 AU Sze G; Kaplowitz N; Ookhtens M; Lu S C
 CS Department of Medicine, University of Southern California School of Medicine, Los Angeles 90033.
 NC DK-30312 (NIDDK)
 DK-45334 (NIDDK)
 SO American journal of physiology, (1993 Dec) 265 (6 Pt 1) G1128-34.
 Journal code: 0370511. ISSN: 0002-9513.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199402
 ED Entered STN: 19940218
 Last Updated on STN: 19980206
 Entered Medline: 19940208
 AB Rat hepatocytes exhibit bidirectional carrier-mediated transport of reduced glutathione (GSH) across the plasma membrane. Transport of GSH has not been well characterized in human-derived cells. We examined Hep G2 cells as a possible human liver model for GSH homeostasis. Hep G2 cell GSH averaged $25.9 \pm 1.4 \text{ nmol}/10^6 \text{ cells}$. When Hep G2 cells were incubated in buffer, no GSH appeared in the medium over 2 h. However, after pretreatment with acivicin to inhibit gamma-glutamyl transpeptidase activity, GSH efflux was unmasked and measured $30 \pm 4 \text{ pmol} \times 10^6 \text{ cells}^{-1} \times \text{min}^{-1}$, which is comparable to rat hepatocytes. GSH efflux was inhibited by sulfobromophthalein GSH adduct (BSP-GSH) and cystathionine, agents that inhibit sinusoidal efflux in the rat, and was stimulated by adenosine 3',5'-cyclic monophosphate-dependent agents. GSH uptake was measured after cells were pretreated with acivicin and buthionine sulfoximine to prevent breakdown of GSH and resynthesis of GSH from precursors, respectively. In the presence of 4 microCi/ml of [³⁵S]GSH and 10 mM unlabeled GSH, GSH uptake was linear up to 45 min and did not require Na⁺ or Cl⁻. GSH uptake exhibited saturability with a maximal velocity of $4.15 \pm 0.23 \text{ nmol} \cdot \text{mg}^{-1} \times 30 \text{ min}^{-1}$, a Michaelis constant of $2.36 \pm 0.26 \text{ mM}$, and two interactive transport sites. BSP-GSH cis-inhibited GSH uptake in a dose-dependent manner with an inhibitory constant of $0.46 \pm 0.05 \text{ mM}$. Inhibition by BSP-GSH (1 mM) of GSH uptake was through a single inhibitor site and was overcome at > 10 mM GSH, which is consistent with competitive inhibition. Similar to the rat, 10 mM extracellular GSH trans-stimulated GSH efflux. These findings may be important in gaining better insights into GSH homeostasis in human liver cells.
 CT Biological Transport
 Bucladesine: PD, pharmacology
 Cell Line
 *Cell Membrane: ME, metabolism
 Cholera Toxin: PD, pharmacology
 *Glutathione: ME, metabolism
 Glutathione: PD, pharmacology
 Hepatoblastoma
 Homeostasis
 Humans
 Isoxazoles: PD, pharmacology
 Kinetics
 *Liver: ME, metabolism
 Liver Neoplasms
 Research Support, U.S. Gov't, P.H.S.
 Sulfobromophthalein: PD, pharmacology
 Tumor Cells, Cultured
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 gamma-Glutamyltransferase: ME, metabolism
 RN 297-83-6 (Sulfobromophthalein); 362-74-3 (Bucladesine); 52583-41-2

(acivicin); 52682-84-5 ((sulfonylbenzophenone)glutathione conjugate);
 70-18-8 (Glutathione); 9012-63-9 (Cholera Toxin)
 CN 0 (Isoxazoles); EC 2.3.2.2
 (gamma-Glutamyltransferase)

L30 ANSWER 15 OF 16 MEDLINE on STN
 AN 90297270 MEDLINE
 DN PubMed ID: 1972865
 TI Glutathione catabolism by the ischemic rat kidney.
 AU Slusser S O; Grotto L W; Martin L F; Scaduto R C Jr
 CS Department of Surgery, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey 17033.
 NC DK-40069 (NIDDK)
 HL-01502 (NHLBI)
 SO American journal of physiology, (1990 Jun) 258 (6 Pt 2)
 F1546-53.
 Journal code: 0370511. ISSN: 0002-9513.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199008
 ED Entered STN: 19900907
 Last Updated on STN: 20000303
 Entered Medline: 19900802
 AB The glutathione (GSH) content of rat kidney decreases after cessation of blood flow, falling to 40% of control levels 35 min after renal artery occlusion [R. C. Scaduto, Jr., V. H. Gattone II, L. W. Grotto, J. Wertz, and L. F. Martin. Am. J. Physiol. 255 (Renal Fluid Electrolyte Physiol. 24): F911-F921, 1988]. Renal GSH levels remained depressed for at least 2 h after resumption of blood flow. Because GSH functions in the removal of free radicals, and lipid peroxidation is a free radical-initiated process that occurs in the ischemic kidney, we investigated the fate of this GSH pool in the ischemic kidney. Using high-performance liquid chromatography to measure thiols, we found the loss of GSH to be associated with a stoichiometric accumulation of cysteine in the kidney. Moreover, preischemic labeling of the renal GSH pool with ³⁵S led to accumulation of [³⁵S]cysteine during ischemia that had the same specific activity as that of tissue GSH. Formation of cysteine during ischemia was suppressed in rats pretreated with acivicin, an inhibitor of gamma-glutamyltransferase (gamma-GT), although the degree of suppression was small in comparison to the extent of gamma-GT inhibition. During the initial 2 min of blood reflow after ischemia, tissue cysteine returned to control levels, and a transient increase in the cysteine content of renal venous blood was observed. After ischemia, renal GSH levels remained depressed, but postischemic GSH levels could be increased by administration of N-acetylcysteine during the ischemic period. (ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Male
 Acetylcysteine: PD, pharmacology
 Animals
 Antimetabolites: PD, pharmacology
 Cysteine: ME, metabolism
 *Glutathione: ME, metabolism
 *Ischemia: ME, metabolism
 Isoxazoles: PD, pharmacology
 *Kidney: BS, blood supply
 Kidney: ME, metabolism
 Rats
 Reperfusion
 Research Support, Non-U.S. Gov't
 Research Support, U.S. Gov't, P.H.S.
 Sulfhydryl Compounds: ME, metabolism
 gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 52-90-4 (Cysteine); 52583-41-2 (acivicin); 616-91-1

CN (Acetylcysteine); 70-18-8 (Glutathione)
 0 (Antimetabolites); 0 (Isoxazoles); 0 (Sulphydryl Compounds); EC
 2.3.2.2 (gamma-
Glutamyltransferase)

L30 ANSWER 16 OF 16 MEDLINE on STN
 AN 80146834 MEDLINE
 DN PubMed ID: 6102405
 TI The inhibition of gamma-glutamyl
 transpeptidase from human pancreatic carcinoma cells by (alpha
 S,5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT
 -125; NSC-163501).
 AU Allen L; Meck R; Yunis A
 SO Research communications in chemical pathology and pharmacology, (1980
 Jan) 27 (1) 175-82.
 Journal code: 0244734. ISSN: 0034-5164.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 198005
 ED Entered STN: 19900315
 Last Updated on STN: 19950206
 Entered Medline: 19800514
 AB AT-125, (alpha S, 5S)-alpha-amino-3-chloro-4,5-dihydro-
 5-isoxazoleacetic acid, at a concentration of 5 microM was found to
 inhibit the growth of human pancreatic carcinoma cells (MIA PaCa-2) by 78%
 after 72 hours in continuous culture. It was found that MIA PaCa-2
 gamma-glutamyl transpeptidase (10
 nmol/min/10(6) cells) was irreversibly inactivated by AT-
 125 with an inactivation half-life of 80 minutes at 450 microM.
 CT *Antibiotics, Antineoplastic: PD, pharmacology
 Cells, Cultured
 *Glycine: AA, analogs & derivatives
 Glycine: PD, pharmacology
 Half-Life
 Humans
 *Isoxazoles: PD, pharmacology
 *Oxazoles: PD, pharmacology
 *Pancreatic Neoplasms: EN, enzymology
 Research Support, U.S. Gov't, P.H.S.
 Time Factors
 *gamma-Glutamyltransferase: AI, antagonists & inhibitors
 RN 52583-41-2 (acivicin); 56-40-6 (Glycine)
 CN 0 (Antibiotics, Antineoplastic); 0 (Isoxazoles); 0 (Oxazoles); EC
 2.3.2.2 (gamma-
Glutamyltransferase)

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L40 ANSWER 1 OF 1 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 2001288286 EMBASE
 TI Enhanced gamma-glutamyl transpeptidase

expression and superoxide production in *Mpv17(-/-)* glomerulosclerosis mice.

AU Wagner G.; Stettmaier K.; Bors W.; Sies H.; Wagner E.-M.; Reuter A.; Weiher H.

CS G. Wagner, Inst. fur Physiol. Chemie I, Heinrich-Heine-Universitat, D-40001 Dusseldorf, Germany

SO Biological Chemistry, (2001) Vol. 382, No. 7, pp. 1019-1025.

Refs: 49
ISSN: 1431-6730 CODEN: BICHF3

CY Germany

DT Journal; Article

FS 028 Urology and Nephrology
029 Clinical Biochemistry

LA English

SL English

ED Entered STN: 20010830
Last Updated on STN: 20010830

AB Recently, γ -glutamyl transpeptidase, which initiates cleavage of extracellular glutathione, has been shown to promote oxidative damage to cells. Here we examined a murine disease model of glomerulosclerosis, involving loss of the *Mpv17* gene coding for a peroxisomal protein. In *Mpv17(-/-)* cells, enzyme activity and mRNA expression (examined by quantitative RT-PCR) of membrane-bound γ -glutamyl transpeptidase were increased, while plasma glutathione peroxidase and superoxide dismutase levels were lowered. Superoxide anion production in these cells was increased as documented by electron spin resonance spectroscopy. In the presence of Mn(III)tetrakis(4-benzoic acid)porphyrin, the activities of γ -glutamyl transpeptidase and plasma glutathione peroxidase were unchanged, suggesting a relationship between enzyme expression and the amount of reactive oxygen species. Inhibition of γ -glutamyl transpeptidase by acivicin reverted the lowered plasma glutathione peroxidase and superoxide dismutase activities, indicating reciprocal control of gene expression for these enzymes.

CT Medical Descriptors:
 *glomerulosclerosis
 protein expression
 protein degradation
 oxidative stress
 genetic code
 peroxisome
 enzyme activity
 reverse transcription polymerase chain reaction
 blood level
 electron spin resonance
 gene expression regulation
 nonhuman
 mouse
 animal experiment
 animal model
 controlled study
 animal cell
 article
 priority journal
 Drug Descriptors:
 * γ -glutamyltransferase: EC, endogenous compound
 *superoxide dismutase: EC, endogenous compound
 glutathione peroxidase: EC, endogenous compound
 cell protein: EC, endogenous compound
Mpv 17 protein: EC, endogenous compound
 messenger RNA: EC, endogenous compound
 porphyrin derivative
 manganese(III)tetrakis(4 benzoic acid)porphyrin
 reactive oxygen metabolite: EC, endogenous compound
 acivicin

RN unclassified drug
 (gamma glutamyltransferase) 85876-02-4; (superoxide dismutase)
 37294-21-6, 9016-01-7, 9054-89-1; (glutathione peroxidase) 9013-66-5; (
 acivicin) 42228-92-2

=> d all 143 tot

L43 ANSWER 1 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN

AN 2000416962 EMBASE

TI The species-dependent metabolism of Efavirenz produces a nephrotoxic
 glutathione conjugate in rats.

AU Mutlib A.E.; Gerson R.J.; Meunier P.C.; Haley P.J.; Chen H.; Gan L.S.;
 Davies M.H.; Gemzik B.; Christ D.D.; Krahn D.F.; Markwalder J.A.; Seitz
 S.P.; Robertson R.T.; Miwa G.T.

CS A.E. Mutlib, Drug Metabol./Pharmacokinetics Sec., DuPont Pharmaceuticals
 Company, Stine-Haskell Research Center, Elkton Road, Newark, DE 19714,
 United States

SO Toxicology and Applied Pharmacology, (15 Nov 2000) Vol. 169, No. 1, pp.
 102-113.

Refs: 52

ISSN: 0041-008X CODEN: TXAPA

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy

028 Urology and Nephrology

030 Pharmacology

037 Drug Literature Index

052 Toxicology

LA English

SL English

ED Entered STN: 20001221

Last Updated on STN: 20001221

AB Efavirenz, a potent nonnucleoside reverse transcriptase inhibitor widely
 prescribed for the treatment of HIV infection, produces renal tubular
 epithelial cell necrosis in rats but not in cynomolgus monkeys or humans.
 This species selectivity in nephrotoxicity could result from differences
 in the production or processing of reactive metabolites, or both. A
 detailed comparison of the metabolites produced by rats, monkeys, and
 humans revealed that rats produce a unique glutathione adduct. The
 mechanism of formation and role of this glutathione adduct in the renal
 toxicity were investigated using both chemical and biochemical probes.
 Efavirenz was labeled at the methine position on the cyclopropyl ring with
 the stable isotope deuterium, effectively reducing the formation of the
 cyclopropanol metabolite, an obligate precursor to the glutathione adduct.
 This substitution markedly reduced both the incidence and severity of
 nephrotoxicity as measured histologically. Further processing of this
 glutathione adduct was also important in producing the lesion and was
 demonstrated by inhibiting γ - glutamyltranspeptidase with
 acivicin pretreatment (10 mg/kg, IV) prior to dosing with
 efavirenz. Again, both the incidence and severity of the nephrotoxicity
 were reduced, such that four of nine rats given acivicin were
 without detectable lesions. These studies provide compelling evidence
 that a species-specific formation of glutathione conjugate(s) from
 efavirenz is involved in producing nephrotoxicity in rats. Mechanisms are
 proposed for the formation of reactive metabolites that could be
 responsible for the renal toxicity observed in rats. (C) 2000 Academic
 Press.

CT Medical Descriptors:

*glutathione metabolism

*nephrotoxicity: ET, etiology

*kidney tubule necrosis: ET, etiology

species difference

kidney tubule epithelium

histopathology

morbidity
 disease severity
 drug mechanism
 drug structure
 enzyme inhibition
 drug urine level
 drug effect
 drug metabolism
 nonhuman
 male
 rat
 animal experiment
 animal model
 controlled study
 animal tissue
 article
 Drug Descriptors:
 *efavirenz: TO, drug toxicity
 *efavirenz: PD, pharmacology
 *RNA directed DNA polymerase inhibitor: TO, drug toxicity
 *RNA directed DNA polymerase inhibitor: PD, pharmacology
 *acivicin: PD, pharmacology
 *glutathione derivative: TO, drug toxicity
 *glutathione derivative: EC, endogenous compound
 cyclopropanecarboxylic acid derivative
 deuterium
 gamma glutamyltransferase: EC, endogenous compound
 drug metabolite: TO, drug toxicity
 glutathione: EC, endogenous compound

RN (efavirenz) 154598-52-4; (acivicin) 42228-92-2;
 (deuterium) 7782-39-0; (gamma glutamyltransferase) 85876-02-4;
 (glutathione) 70-18-8

CO Du Pont

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AN 2000234081 EMBASE

TI Contribution of γ glutamyl transpeptidase to oxidative damage of ischemic rat kidney.

AU Cutrin J.C.; Zingaro B.; Camandola S.; Boveris A.; Pompella A.; Poli G.

CS Dr. J.C. Cutrin, Universita di Torino, Dipto. di Sci. Cliniche e Biologiche, ASL San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Torino, Italy. juan.cutrin@sluigi.unito.it

SO Kidney International, (2000) Vol. 57, No. 2, pp. 526-533.

Refs: 40

ISSN: 0085-2538 CODEN: KDYIA5

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology

LA English

SL English

ED Entered STN: 20000720

Last Updated on STN: 20000720

AB Background. A variety of mechanisms have been considered in the pathogenesis of the cell damage occurring in the kidney that is undergoing transient ischemia. However, little information is available about the role of oxidative stress in building up the tissue injury in the hypoxic organ during short-term ischemia. Methods. After a standard brief period (25 min) of unilateral kidney ischemia in rats, pretreated or not with acivicin (60 μ mol/L/kg i.v.), tissue samples from both ischemic and non-ischemic kidneys were obtained to measure malondialdehyde (MDA) and glutathione (GSH) content, γ glutamyl transpeptidase (GGT) activity by spectrophotometry, localization and intensity of enzyme activity, and tissue damage by histochemistry. Results. GGT activity was found to be

increased in both cortical and medullar zones of the ischemic kidneys, where the GSH level was only slightly decreased and the MDA level, in contrast, was markedly increased; in parallel, the cytosolic volume of the proximal tubular (PT) cells showed a significant increment. The animal pretreatment with acivicin, a specific inhibitor of GGT , besides preventing the up-regulation of the enzyme during ischemia, afforded good protection against the observed changes of MDA and GSH tissue levels, as well as of tubular cell volume. Conclusions. Ex vivo data supporting a net pro-oxidant effect of up-regulated GGT during short- term ischemia of rat kidney have been obtained. The enzyme stimulation appears to contribute to the renal morphological damage exerted by a brief hypoxic condition at the level of PT cells. The actual impact on kidney function by GGT-dependent oxidative damage during transient ischemia and the potential protective action of GGT inhibitors require subsequent investigation.

CT Medical Descriptors:

- *kidney ischemia
- enzyme activity
- enzyme localization
- histochemistry
- spectrophotometry
- nonhuman
- male
- rat
- animal experiment
- animal model
- controlled study
- animal tissue
- article
- priority journal

Drug Descriptors:

- *gamma glutamyltransferase: EC, endogenous compound
- acivicin
- malonaldehyde: EC, endogenous compound
- glutathione peroxidase: EC, endogenous compound
- (gamma glutamyltransferase) 85876-02-4; (acivicin) 42228-92-2; (malonaldehyde) 542-78-9; (glutathione peroxidase) 9013-66-5

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on STN

AN 1999298306 EMBASE

TI Glutathione-dependent metabolism of cis-3-(9H-purin-6-ylthio)acrylic acid to yield the chemotherapeutic drug 6-mercaptopurine: Evidence for two distinct mechanisms in rats.

AU Gunnarsdottir S.; Elfarra A.A.

CS A.A. Elfarra, Dept. of Comparative Biosciences, University of Wisconsin, School of Veterinary Medicine, 2015 Linden Dr., Madison, WI 53706, United States. elfarraa@svm.vetmed.wisc.edu

SO Journal of Pharmacology and Experimental Therapeutics, (1999) Vol. 290, No. 3, pp. 950-957.

Refs: 39

ISSN: 0022-3565 CODEN: JPETAB

CY United States

DT Journal; Article

FS 030 Pharmacology
037 Drug Literature Index

LA English

SL English

ED Entered STN: 19990910

Last Updated on STN: 19990910

AB cis-3-(9H-Purin-6-ylthio)acrylic acid (PTA) is a structural analog of azathioprine, a prodrug of the antitumor and immunosuppressive drug 6-mercaptopurine (6-MP). In this study, we examined the in vitro and in vivo metabolism of PTA in rats. Two metabolites of PTA, 6-MP and the major metabolite, S-(9H-purin-6-yl)glutathione (PG), were formed in a

time- and GSH-dependent manner in vitro. Formation of 6-MP and PG occurred nonenzymatically, but 6-MP formation was enhanced 2-and 7-fold by the addition of liver and kidney homogenates, respectively. Purified rat liver glutathione S-transferases enhanced 6-MP formation from PTA by 1.8-fold, whereas human recombinant α , μ , and π isozymes enhanced 6-MP formation by 1.7-, 1.3-, and 1.3-fold, respectively. In kidney homogenate incubations, PG accumulation was only observed during the first 15 min because of further metabolism by γ -glutamyl-transpeptidase, dipeptidase, and β -lyase to yield 6-MP, as indicated by the use of the inhibitors acivicin and aminoxy-acetic acid. Based on these results and other lines of evidence, two different GSH-dependent pathways are proposed for 6-MP formation: an indirect pathway involving PG formation and further metabolism to 6-MP, and a direct pathway in which PTA acts as a Michael acceptor. HPLC analyses of urine of rats treated i.p. with PTA (100 mg/kg) showed that 6-MP was formed in vivo and excreted in urine without apparent liver or kidney toxicity. Collectively, these studies show that PTA is metabolized to 6-MP both in vitro and in vivo and may therefore be a useful prodrug of 6-MP.

- CT Medical Descriptors:
 *glutathione metabolism
 *cancer chemotherapy
 drug mechanism
 antineoplastic activity
 immunosuppressive treatment
 drug metabolism
 enzyme subunit
 liver homogenate
 nephrotoxicity
 structure analysis
 human
 nonhuman
 rat
 animal model
 human cell
 animal cell
 article
 priority journal
 Drug Descriptors:
 *glutathione: EC, endogenous compound
 *azathioprine derivative: PD, pharmacology
 *3 (9h purin 6 ylthio)acrylic acid: PD, pharmacology
 *mercaptopurine: PD, pharmacology
 gamma glutamyltransferase: EC, endogenous compound
 dipeptidase: EC, endogenous compound
 acivicin: PD, pharmacology
 aminoxyacetic acid: PD, pharmacology
 (glutathione) 70-18-8; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1;
 (gamma glutamyltransferase) 85876-02-4; (dipeptidase) 9031-99-6;
 (acivicin) 42228-92-2; (aminoxyacetic acid)
 2921-14-4, 645-88-5
 CO Sigma (United States)
- L43 ANSWER 4 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
- AN 1999027532 EMBASE
- TI Synthesis of the antioxidant glutathione in neurons: Supply by astrocytes of CysGly as precursor for neuronal glutathione.
- AU Dringen R.; Pfeiffer B.; Hamprecht B.
- CS Dr. R. Dringen, Phys.-Chemisches Inst. der Univ., Hoppe-Seyler-Strasse 4,
 D-72076 Tubingen, Germany
- SO Journal of Neuroscience, (15 Jan 1999) Vol. 19, No. 2, pp. 562-569.
 Refs: 49
 ISSN: 0270-6474 CODEN: JNRSDS
- CY United States
- DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
 008 Neurology and Neurosurgery
 029 Clinical Biochemistry

LA English
 SL English
 ED Entered STN: 19990218
 Last Updated on STN: 19990218

AB Deficiency of the antioxidant glutathione in brain appears to be connected with several diseases characterized by neuronal loss. To study neuronal glutathione metabolism and metabolic interactions between neurons and astrocytes in this respect, neuron-rich primary cultures and transient cocultures of neurons and astroglial cells were used. Coincubation of neurons with astroglial cells resulted within 24 hr of incubation in a neuronal glutathione content twice that of neurons incubated in the absence of astroglial cells. In cultured neurons, the availability of cysteine limited the cellular level of glutathione. During a 4 hr incubation in a minimal medium lacking all amino acids except cysteine, the amount of neuronal glutathione was doubled. Besides cysteine, also the dipeptides CysGly and γ GluCys were able to serve as glutathione precursors and caused a concentration-dependent increase in glutathione content. Concentrations giving half-maximal effects were 5, 5, and 200 μ M for cysteine, CysGly, and γ GluCys, respectively. In the transient cocultures, the astroglia-mediated increase in neuronal glutathione was suppressed by acivicin, an inhibitor of the astroglial ectoenzyme γ -glutamyl transpeptidase, which generates CysGly from glutathione. These data suggest the following metabolic interaction in glutathione metabolism of brain cells: the ectoenzyme γ -glutamyl transpeptidase uses as substrate the glutathione released by astrocytes to generate the dipeptide CysGly that is subsequently used by neurons as precursor for glutathione synthesis.

CT Medical Descriptors:
 *astrocyte
 *glutathione metabolism
 *oxidative stress
 *nerve degeneration: ET, etiology
 nerve cell
 macroglia
 coculture
 biosynthesis
 antioxidant activity
 cell viability
 cell lysate
 nonhuman
 rat
 controlled study
 animal cell
 embryo
 article
 priority journal
 Drug Descriptors:
 *glutathione: EC, endogenous compound
 *antioxidant: EC, endogenous compound
 *cysteinylglycine
 *dipeptide
 gamma glutamyltransferase: EC, endogenous compound
 cysteine
 acivicin

RN (glutathione) 70-18-8; (gamma glutamyltransferase) 85876-02-4;
 (cysteine) 4371-52-2, 52-89-1, 52-90-4; (acivicin)
 42228-92-2

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 on STN
 AN 96356214 EMBASE
 DN 1996356214

TI Cisplatin nephrotoxicity: Inhibition of γ -glutamyl transpeptidase blocks the nephrotoxicity of cisplatin without reducing platinum concentrations in the kidney.
 AU Hanigan M.H.; Gallagher B.C.; Taylor P.T. Jr.; Grover L.; Eddy G.L.
 CS School of Medicine, University of Virginia, Box 439, Charlottesville, VA 22908, United States
 SO American Journal of Obstetrics and Gynecology, (1996) Vol. 175, No. 2, pp. 270-274.
 ISSN: 0002-9378 CODEN: AJOGAH
 CY United States
 DT Journal; Conference Article
 FS 016 Cancer
 028 Urology and Nephrology
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 ED Entered STN: 961218
 Last Updated on STN: 961218
 AB OBJECTIVE: Inhibition of γ -glutamyl transpeptidase activity by acivicin or a large bolus of intravenous glutathione blocks the nephrotoxicity of cisplatin. The purpose of this study was to determine whether these compounds inhibit nephrotoxicity by reducing the amount of platinum retained by the kidney.
 STUDY DESIGN: The platinum concentration in urine and kidney of cisplatin-treated rats was determined by graphite furnace atomic absorption spectroscopy. Tissues from three experimental groups of rats were analyzed. The first group was treated with a nephrotoxic dose of cisplatin. The second group was treated with acivicin before cisplatin. The third group received a bolus of glutathione before cisplatin. Urine collected for 3 hours after the injection of cisplatin and kidney tissue from animals 5 days after treatment were analyzed for platinum content.
 RESULTS: Urine from animals pretreated with acivicin had the same concentration of platinum as that of control animals treated with cisplatin alone. Analysis of kidney tissue, blood urea nitrogen and serum creatinine 5 days after treatment showed that pretreatment with acivicin or glutathione blocked the nephrotoxicity of cisplatin. However, these agents did not alter the concentration of platinum in the kidney.
 CONCLUSIONS: The data in this study reveal that pretreatment with acivicin or glutathione does not block the uptake of platinum into the kidney nor do these agents reduce the concentration of platinum retained by the kidney. The mechanism by which these agents may inhibit the nephrotoxicity of cisplatin is discussed.
 CT Medical Descriptors:
 *nephrotoxicity: PC, prevention
 animal experiment
 animal tissue
 atomic absorption spectrometry
 conference paper
 controlled study
 creatinine blood level
 drug tissue level
 drug uptake
 drug urine level
 enzyme inhibition
 human
 intravenous drug administration
 kidney
 male
 priority journal
 rat
 urea nitrogen blood level
 Drug Descriptors:
 *acivicin: DO, drug dose
 *acivicin: PD, pharmacology

*cisplatin: DO, drug dose
 *cisplatin: TO, drug toxicity
 *cisplatin: PD, pharmacology
 *gamma glutamyltransferase: EC, endogenous compound
 *glutathione: AD, drug administration
 *glutathione: DO, drug dose
 *glutathione: PD, pharmacology
 *platinum: CR, drug concentration
 creatinine: EC, endogenous compound
 RN (acivicin) 42228-92-2; (cisplatin) 15663-27-1,
 26035-31-4, 96081-74-2; (gamma glutamyltransferase) 85876-02-4;
 (glutathione) 70-18-8; (platinum) 7440-06-4; (creatinine) 19230-81-0,
 60-27-5

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on STN

AN 94362282 EMBASE

DN 1994362282

TI Inhibition of γ -glutamyl transpeptidase activity by acivicin in vivo protects the kidney from cisplatin-induced toxicity.

AU Hanigan M.H.; Gallagher B.C.; Taylor Jr. P.T.; Large M.K.

CS Department of Cell Biology, School of Medicine, University of Virginia, Charlottesville, VA 22908, United States

SO Cancer Research, (1994) Vol. 54, No. 22, pp. 5925-5929.

ISSN: 0008-5472 CODEN: CNREA8

CY United States

DT Journal; Article

FS 016 Cancer

028 Urology and Nephrology

029 Clinical Biochemistry

030 Pharmacology

037 Drug Literature Index

LA English

SL English

ED Entered STN: 950112

Last Updated on STN: 950112

AB Cisplatin [cis-dichlorodiammineplatinum(II)] is a widely used chemotherapeutic drug that is toxic to the proximal tubule cells of the kidney. γ -Glutamyl transpeptidase (GGT) is localized to the luminal surface of the renal proximal tubules. GGT catalyzes the initial step in the metabolism of glutathione-conjugated drugs to mercapturic acids, some of which are severely nephrotoxic. We proposed that the nephrotoxicity of cisplatin was dependent on the cleavage of a cisplatin-glutathione conjugate by GGT. To test this hypothesis, renal GGT activity was blocked in male Sprague-Dawley rats by acivicin, a non-competitive inhibitor of GGT. Treatment with cisplatin alone caused extensive acute necrosis of the proximal tubules, but the proximal tubule cells appeared normal in rats treated with acivicin prior to cisplatin. Blood urea nitrogen and serum creatinine levels confirmed the protective effect of acivicin. Glutathione is a physiological substrate for GGT.

Administration of an 83-fold excess of glutathione 30 min prior to cisplatin also inhibited cisplatin-induced nephrotoxicity. These data provide important new evidence that a large bolus of glutathione blocks the nephrotoxicity of cisplatin by competitively inhibiting GGT.

These results indicate that cisplatin is conjugated to glutathione in vivo. The platinum-glutathione conjugate is nontoxic until metabolized by the proximal tubule cells. Formation of the nephrotoxic derivative of cisplatin requires GGT activity.

CT Medical Descriptors:

*acute kidney tubule necrosis: ET, etiology

*kidney proximal tubule

animal model

animal tissue

article
 body weight
 controlled study
 drug conjugation
 drug metabolism
 enzyme activity
 enzyme inhibition
 intravenous drug administration
 nonhuman
 priority journal
 protection
 rat

Drug Descriptors:

*acivicin: AD, drug administration
 *acivicin: CB, drug combination
 *acivicin: DO, drug dose
 *acivicin: IT, drug interaction
 *acivicin: PD, pharmacology
 *cisplatin: TO, drug toxicity
 *cisplatin: DO, drug dose
 *cisplatin: IT, drug interaction
 *cisplatin: CB, drug combination
 *gamma glutamyltransferase: EC, endogenous compound

acetylcysteine
 creatinine: EC, endogenous compound
 glutathione
 nitrogen: EC, endogenous compound
 urea: EC, endogenous compound

RN (acivicin) 42228-92-2; (cisplatin) 15663-27-1,
 26035-31-4, 96081-74-2; (gamma glutamyltransferase) 85876-02-4;
 (acetylcysteine) 616-91-1; (creatinine) 19230-81-0, 60-27-5; (glutathione)
 70-18-8; (nitrogen) 7727-37-9; (urea) 57-13-6

CN (1) At 125; (2) Platinol

CO (1) Sigma (United States); (2) Bristol (United States)

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 on STN

AN 93009711 EMBASE

DN 1993009711

TI The effects of 2,3,5-(triglutathion-S-yl)hydroquinone on renal
 mitochondrial respiratory function in vivo and in vitro: Possible role in
 cytotoxicity.

AU Hill B.A.; Monks T.J.; Lau S.S.

CS Division of Pharmacology/Toxicology, College of Pharmacy, University of
 Texas, Austin, TX 78712, United States

SO Toxicology and Applied Pharmacology, (1992) Vol. 117, No. 2, pp. 165-171.
 ISSN: 0041-008X CODEN: TXAPA

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
 028 Urology and Nephrology
 029 Clinical Biochemistry
 052 Toxicology
 037 Drug Literature Index

LA English

SL English

ED Entered STN: 930207
 Last Updated on STN: 930207

AB Administration of 2,3,5-(triglutathion-S-yl)hydroquinone
 [2,3,5-(triGSyl)HQ] to rats causes severe renal proximal tubular necrosis.
 Although the cellular target(s) for 2,3,5-(triGSyl)HQ is not known,
 substantial evidence implicates mitochondria as the primary cellular
 target for aliphatic S-conjugates. To determine whether mitochondria are
 targets for 2,3,5-(triGSyl)HQ, the in vivo and in vitro effects of this
 conjugate on rat renal mitochondria (RRM) were investigated. In vitro
 exposure of RRM to 2,3,5-(triGSyl)HQ inhibited site I-supported

respiration to a much greater extent than site II-supported respiration. Inhibition of mitochondrial function, as manifested by decreases in the respiratory control ratios, were a consequence of significant elevations in state 4 respiration. Inhibition of constitutive γ -GT activity with AT-125 had no effect on the ability of 2,3,5-(triGSyl)HQ to decrease mitochondrial function. The effects of 2,3,5-(triGSyl)HQ on mitochondrial function *in vivo* were subsequently assessed. Shortly (0.5-2.0 hr) following administration of 2,3,5-(triGSyl)HQ (20 μ mol/kg, iv) to rats, a significant elevation of state 4 respiration was observed. Thereafter (4-16 hr) state 4 respiration returned to control values and state 3 respiration became significantly depressed. A total collapse in RRM function occurred by 24 hr. The effects of 2,3,5-(triGSyl)HQ on state 4 respiration preceded significant elevations in blood urea nitrogen, which occurred at 8 hr. However, pretreatment of animals with probenecid, an inhibitor of organic anion transport, caused a significant decrease in the 2,3,5-(triGSyl)HQ-mediated elevations in state 4 respiration at 1 hr, without preventing the subsequent development of renal necrosis. In contrast, AT-125, which protected animals from 2,3,5-(triGSyl)HQ-mediated nephrotoxicity, had no effect on the early (1 hr) elevations in state 4 respiration but did prevent the later (8 hr) decreases in state 3 respiration. The data suggest that the early elevation in state 4 respiration observed *in vivo* is unlikely to contribute to 2,3,5-(triGSyl)HQ-mediated nephrotoxicity. The relationship between the decrease in state 3 respiration seen at later time points and the subsequent development of toxicity require further study before a cause and effect relationship can be determined..

CT Medical Descriptors:

- *cytotoxicity
- *kidney tubule necrosis
- *mitochondrial respiration
- animal experiment
- animal tissue
- article
- concentration response
- controlled study
- intraperitoneal drug administration
- male
- nonhuman
- priority journal
- rat
- urea nitrogen blood level

Drug Descriptors:

- 2,3,5 tris(glutathion s yl)hydroquinone: TO, drug toxicity
- acivicin: PD, pharmacology
- gamma glutamyltransferase: EC, endogenous compound
- hydroquinone: TO, drug toxicity
- probenecid: PD, pharmacology
- urea: EC, endogenous compound
- unclassified drug

RN (acivicin) 42228-92-2; (gamma glutamyltransferase) 85876-02-4; (hydroquinone) 123-31-9;
 (probenecid) 57-66-9; (urea) 57-13-6

CN (1) At 125

CO (1) National cancer institute

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AN 91267891 EMBASE

DN 1991267891

TI Inhibition of γ -glutamyl transpeptidase
 potentiates the nephrotoxicity of glutathione-conjugated chlorohydroquinones.

AU Mertens J.J.W.M.; Temmink J.H.M.; Van Bladeren P.J.; Jones T.W.; Lo H.-H.;
 Lau S.S.; Monks T.J.

CS Division of Pharmacology and Toxicology, College of Pharmacy, University

of Texas, Austin, TX 78712, United States
 SO Toxicology and Applied Pharmacology, (1991) Vol. 110, No. 1, pp. 45-60.
 ISSN: 0041-008X CODEN: TXAPA

CY United States
 DT Journal; Article
 FS 028 Urology and Nephrology
 029 Clinical Biochemistry
 035 Occupational Health and Industrial Medicine
 052 Toxicology
 037 Drug Literature Index

LA English
 SL English
 ED Entered STN: 911216
 Last Updated on STN: 911216

AB Administration of either 2,5-dichloro-3-(glutathion-S-yl)-1,4-benzoquinone (DC-[GSyl]BQ) or 2,5,6-trichloro-3-(glutathion-S-yl)-1,4-benzoquinone (TC-[GSyl]BQ) to male Sprague-Dawley rats caused dose-dependent (50-200 µmol/kg; iv) renal proximal tubular necrosis, as evidenced by elevations in blood urea nitrogen (BUN), and in the urinary excretion of lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GT) and glucose. Renal proximal tubular necrosis was also confirmed by histological examination of kidney slices prepared from DC-(GSyl)BQ- and TC-(GSyl)BQ-treated animals. Administration of the corresponding hydroquinone conjugates (DC-[GSyl]HQ and TC-[GSyl]HQ), prepared by reducing the quinones with a threefold molar excess of ascorbic acid, resulted in a substantial increase in nephrotoxicity. Moreover, in contrast to other glutathione (GSH)-conjugated hydroquinones, the nephrotoxicity of both DC-(GSyl)HQ and TC-(GSyl)HQ was potentiated when rats were pretreated with AT-125, an irreversible inhibitor of γ-GT. Neither the quinone-GSH nor the hydroquinone-GSH conjugates caused any effect on liver histology or serum glutamate-pyruvate transaminase levels. The results suggest that coadministration of ascorbic acid with DC-(GSyl)BQ or TC-(GSyl)BQ decreases their interactions with extrarenal nucleophiles, including plasma proteins, and thus increases the concentration of the conjugates delivered to the kidney, and hence toxicity. Furthermore the ability of AT-125 to potentiate the nephrotoxicity of DC-(GSyl)HQ and TC-(GSyl)HQ suggests that metabolism of these conjugates by γ-GT constitutes a detoxication reaction.

CT Medical Descriptors:
 *enzyme inhibition
 *kidney tubule necrosis
 *nephrotoxicity
 animal experiment
 animal tissue
 article
 male
 nonhuman
 priority journal
 rat
 Drug Descriptors:
 *benzoquinone: TO, drug toxicity
 *gamma glutamyltransferase: EC, endogenous compound
 *lactate dehydrogenase: EC, endogenous compound
 acivicin: PD, pharmacology
 ascorbic acid: PD, pharmacology
 glucose: EC, endogenous compound
 lactic acid: EC, endogenous compound
 RN (gamma glutamyltransferase) 85876-02-4; (lactate dehydrogenase) 90001-60-9; (acivicin) 42228-92-2; (ascorbic acid) 134-03-2, 15421-15-5, 50-81-7; (glucose) 50-99-7, 84778-64-3; (lactic acid) 113-21-3, 50-21-5
 CN At 125

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on STN
 AN 90116335 EMBASE
 DN 1990116335
 TI The in vivo disposition of 2-bromo-[14C]hydroquinone and the effect of .
 gamma.-glutamyl transpeptidase inhibition.
 AU Lau S.S.; Monks T.J.
 CS Division of Pharmacology and Toxicology, College of Pharmacy, University
 of Texas, Austin, TX 78712, United States
 SO Toxicology and Applied Pharmacology, (1990) Vol. 103, No. 1, pp. 121-132.
 ISSN: 0041-008X CODEN: TXAPA
 CY United States
 DT Journal; Article
 FS 028 Urology and Nephrology
 029 Clinical Biochemistry
 035 Occupational Health and Industrial Medicine
 052 Toxicology
 037 Drug Literature Index
 LA English
 SL English
 ED Entered STN: 911213
 Last Updated on STN: 911213
 AB We have previously shown that the renal necrosis observed after
 2-bromohydroquinone (2-BrHQ) administration to rats is probably caused by
 the formation of 2-Br-(diglutathion-S-yl)HQ (2-Br-[diGSyl]HQ), since
 injection of this conjugate caused severe proximal tubular necrosis. In
 the present study we report the in vivo metabolism and covalent binding of
 2-[14C]-BrHQ in male Sprague-Dawley rats. The major urinary and biliary
 metabolite was a glucuronide conjugate. In addition, 2-Br-(di-GSyl)HQ,
 2-Br-3-(GSyl)HQ, 2-Br-5-(GSyl)HQ, and 2-Br-6-(GSyl)HQ were all detected as
 urinary and biliary metabolites of 2-BrHQ. The in vivo covalent binding
 of 2-[14C]BrHQ to kidney, pancreas, seminal vesicles, intestine, bone
 marrow, and liver was 21.8, 1.5, 1.2, 4.4, 1.8, and 2.6 nmol/mg protein,
 respectively. γ -Glutamyl transpeptidase
 (γ -GT) activity measured in these tissues was
 947, 159, 55, 31, and 5.5 U/mg. Liver γ -GT
 activity was negligible (0.07 U/mg). Thus, maximum covalent binding and .
 gamma.-GT activity occurred in the kidney. Renal
 covalent binding and γ -GT activity were
 positively correlated with nephrotoxicity. Pretreatment of rats with
 L(α S,5S)- α -amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125)
 inhibited renal γ -GT,
 after 24 hr, by 76%, renal covalent binding by 73%, and 2-BrHQ-mediated
 nephrotoxicity, as assessed by elevations in blood urea nitrogen (BUN), by
 70%. These alterations were accompanied by an increase in the urinary
 excretion of each of the GSH conjugates, an increase in the fecal
 excretion of total radioactivity, and a decrease in plasma radioactivity
 at 24 hr. The present data provide evidence that 2-BrHQ is metabolized in
 vivo to nephrotoxic GSH conjugates. In addition, AT-125
 probably inhibits nephrotoxicity by decreasing the γ -
 GT-mediated renal proximal tubule accumulation of the toxic
 metabolites, thereby facilitating their excretion into urine. Although
 AT-125 inhibited extrarenal γ -GT
 activity by 34-77%, it had variable effects on extrarenal covalent
 binding. Whereas covalent binding to renal tissue is probably mediated by
 reactive metabolites of the isomeric 2-Br-(GSyl)HQ conjugates, binding to
 extrarenal tissue may be mediated by both the conjugates and by
 2-bromohydroquinone per se.
 CT Medical Descriptors:
 *bromohydroquinone
 *nephrotoxicity
 covalent bond
 enzyme inhibition
 rat
 toxicokinetics
 xenobiotic metabolism
 animal experiment

nonhuman
 male
 article
 priority journal
 Drug Descriptors:
 *gamma glutamyltransferase
 radioisotope
 *acivicin
 RN (gamma glutamyltransferase) 85876-02-4; (acivicin)
 42228-92-2
 CN (1) At 125
 CO (1) National cancer institute

L43 ANSWER 10 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
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AN 90100113 EMBASE
 DN 1990100113
 TI Role of γ - glutamyltranspeptidase in renal uptake and
 toxicity of inorganic mercury in mice.
 AU Tanaka T.; Naganuma A.; Imura N.
 CS Department of Public Health, School Pharmaceutical Science, Kitasato
 University, 9-1 Shirokane 5-chome, Minato-ku, Tokyo 108, Japan
 SO Toxicology, (1990) Vol. 60, No. 3, pp. 187-198.
 ISSN: 0300-483X CODEN: TXCYAC

CY Ireland
 DT Journal; Article
 FS 028 Urology and Nephrology
 029 Clinical Biochemistry
 052 Toxicology
 LA English
 SL English
 ED Entered STN: 911213
 Last Updated on STN: 911213

AB The role of renal glutathione (GSH) metabolism as a mediating factor in
 the renal uptake and toxicity of inorganic mercury was investigated in
 mice by preadministering a γ - glutamyltranspeptidase (GGT) inhibitor, acivicin. Pretreatment with
 acivicin (0.25, 1.0 or 2.5 mmol/kg, i.p.) led to a dose-dependent
 decrease in renal mercury content and increases in mercury and GSH
 contents in urine measured 2 h after HgCl₂ injection (18 μ mol/kg,
 i.v.). Acivicin pretreatment also ameliorated the renal and
 lethal toxicity caused by administration of inorganic mercury. Treatment
 of the mice with 1,2-dichloro-4-nitrobenzene (DCNB, 2.5 mmol/kg, i.p.), a
 specific depleter of hepatic GSH, prior to HgCl₂ injection substantially
 reduced renal Hg content and consequently reduced the renal damage. In
 addition, coadministration of GSH (36 μ mol/kg, i.v.) with HgCl₂
 increased the renal Hg content measured 5 min after HgCl₂ injection to 2.6
 fold higher than that of mice treated with HgCl₂ alone. These results
 suggest that renal uptake of inorganic mercury, which is supposedly
 transported to the kidney as a mercury-GSH complex, is dependent on a
 reaction catalyzed by GGT on the outer surface of the renal
 brush border membrane in the same manner as the metabolism of GSH.

CT Medical Descriptors:
 *nephrotoxicity
 bioaccumulation
 kidney
 mouse
 animal experiment
 nonhuman
 male
 article
 priority journal
 Drug Descriptors:
 *gamma glutamyltransferase
 *glutathione
 *mercury

1,2 dichloro 4 nitrobenzene
 acivicin

RN (gamma glutamyltransferase) 85876-02-4; (glutathione) 70-18-8;
 (mercury) 14302-87-5, 7439-97-6; (1,2 dichloro 4 nitrobenzene) 99-54-7; (acivicin) 42228-92-2

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AN 90040167 EMBASE
 DN 1990040167

TI Role of γ - glutamyltranspeptidase and β -lyase in the nephrotoxicity of hexachloro-1,3-butadiene and methyl mercury in mice.

AU De Ceaurriz J.; Ban M.

CS INRS, Avenue de Bourgogne, 54501 Vandoeuvre, France

SO Toxicology Letters, (1990) Vol. 50, No. 2-3, pp. 249-256.
 ISSN: 0378-4274 CODEN: TOLEDS

CY Netherlands

DT Journal; Article

FS 037 Drug Literature Index
 028 Urology and Nephrology
 029 Clinical Biochemistry
 046 Environmental Health and Pollution Control
 052 Toxicology

LA English
 SL English

ED Entered STN: 911213
 Last Updated on STN: 911213

AB Male Swiss OF1 mice received a single oral dose of either 80 mg/kg hexachloro-1,3-butadiene (HCBD) or 80 mg/kg methyl mercury (MeHg). Examination of cryostat kidney sections stained for alkaline phosphatase (APP) revealed damage to about 50% of the proximal tubules after 8 h. Pretreatment with the γ - glutamyltranspeptidase (gamma-GT) inactivator AT-125 (Acivin, 50 mg/kg i.p., plus 50 mg/kg p.o.), reduced the number of damaged tubules by 59 and 58% in mice treated with HCBD and MeHg, respectively. Pretreatment with the two β -lyase inhibitors, amino-oxyacetic acid (AOAA, 3 x 100 mg/kg p.o.) and DL-propargylglycine (PPG, 300 mg/kg i.p. plus 300 mg/kg p.o.), reduced HCBD nephrotoxicity by 46 and 59%, respectively, but did not protect against MeHg nephrotoxicity. The results support a role for γ -GT and β -lyase in the mouse renal toxicity of HCBD and implicate gamma-GT but not β -lyase in MeHg-induced nephrotoxicity in mice.

CT Medical Descriptors:
 *beta lyase
 *nephrotoxicity
 kidney proximal tubule
 mouse
 animal experiment
 nonhuman
 male
 intraperitoneal drug administration
 oral drug administration
 article
 priority journal
 Drug Descriptors:
 *gamma glutamyltransferase
 *hexachlorobutadiene
 *methylmercury
 *acivicin
 *aminoxyacetic acid
 *propargylglycine

RN (gamma glutamyltransferase) 85876-02-4; (hexachlorobutadiene) 87-68-3; (methylmercury) 16056-34-1, 593-74-8; (acivicin) 42228-92-2; (aminoxyacetic acid) 2921-14-4, 645-88-5; (propargylglycine) 58160-95-5

CN (1) At 125
 CO (1) Upjohn; Sigma

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AN 88210892 EMBASE

DN 1988210892

TI Effects of AT-125 on the nephrotoxicity of hexachloro-1,3-butadiene in rats.

AU Davis M.E.

CS Department of Pharmacology and Toxicology, Health Science Center, West Virginia University, Morgantown, WV 26506, United States

SO Toxicology and Applied Pharmacology, (1988) Vol. 95, No. 1, pp. 44-52.
 ISSN: 0041-008X CODEN: TXAPPA

CY United States

DT Journal

FS 028 Urology and Nephrology
 029 Clinical Biochemistry
 052 Toxicology
 030 Pharmacology
 037 Drug Literature Index

LA English

SL English

ED Entered STN: 911211

Last Updated on STN: 911211

AB The role of γ -glutamyl transpeptidase (γ -GTP) in the nephrotoxicity of hexachloro-1,3-butadiene (HCBD) was studied using male Sprague-Dawley rats pretreated with AT-125 (Acivicin; L-(α S, 5S)- α -amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid). Inhibition of γ -GTP by more than 95% did not affect urine output, glomerular filtration rate, or tubular reabsorption of filtrate, sodium, or glucose. Nephrotoxicity observed during the first 24 hr after HCBD was not decreased by inhibition of γ -GTP and beyond 24 hr nephrotoxicity was increased, rather than decreased, in the AT-125-pretreated group. HCBD impairs glucose reabsorption and this was greatly increased in the AT-125-pretreated group, indicating that function of the initial segment of the nephron is impaired by HCBD. Since inhibition of γ -GTP did not protect against HCBD nephrotoxicity, it is concluded that γ -GTP inhibition does not limit the formation of metabolite(s) which cause HCBD nephrotoxicity. Therefore, distribution of γ -glutamyltranspeptidase does not account for the selective nephrotoxicity of hexachloro-1,3-butadiene.

CT Medical Descriptors:

*nephrotoxicity

enzyme inhibition

rat

priority journal

animal experiment

nonhuman

intraperitoneal drug administration

Drug Descriptors:

*gamma glutamyltransferase

*hexachlorobutadiene

*acivicin: DT, drug therapy

RN (gamma glutamyltransferase) 85876-02-4; (hexachlorobutadiene)
 87-68-3; (acivicin) 42228-92-2

CN (1) At 125

CO (1) National cancer institute

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AN 87211012 EMBASE

DN 1987211012

TI Nephrotoxicity of S-(2-chloroethyl)glutathione in the Fischer rat:
 Evidence for γ - glutamyltranspeptidase-independent uptake
 by the kidney.
 AU Kramer R.A.; Foureman G.; Greene K.E.; Reed D.J.
 CS Laboratory of Experimental Therapeutics and Metabolism, Developmental
 Therapeutics Program, National Cancer Institute, Bethesda, MD, United
 States
 SO Journal of Pharmacology and Experimental Therapeutics, (1987) Vol. 242,
 No. 2, pp. 741-748.
 ISSN: 0022-3565 CODEN: JPETAB
 CY United States
 DT Journal
 FS 028 Urology and Nephrology
 052 Toxicology
 030 Pharmacology
 037 Drug Literature Index
 LA English
 AB S-(2-chloroethyl)glutathione (CEG; 270 μ mol/kg) produced renal lesions
 that were confined to the proximal tubules of the outer stripe of the
 outer medulla and were similar to those lesions produced by the cysteine
 analog S-(2-chloroethyl)cysteine or by the nephrotoxic glutathione (GSH)
 adduct of 2-bromohydroquinone. These histopathologic changes in the
 kidney were correlated with alterations in renal function as reflected by
 dose- and time-dependent elevations in blood urea nitrogen levels as well
 as by the increased urinary excretion of protein, glucose and lactate
 dehydrogenase activity. The role of renal GSH metabolism as a mediating
 factor in the nephrotoxicity of these GSH conjugates was investigated by
 administering the γ - glutamyltranspeptidase inhibitor
 AT-125 [L-(α -S,5S)- α -amino-3-chloro-4,5-
 dihydro-5-isoxazoleacetic acid]. Treatment with AT-125
 led to a dose-dependent decrease in renal γ -
 glutamyltranspeptidase activity that correlated inversely with
 increased GSH concentrations in the urine and kidney. Pretreatment with
 AT-125 ameliorated 2-bromohydroquinone-induced renal
 toxicity but did not protect against the CEG-induced renal lesion. In
 fact, pretreatment with AT-125 produced a
 dose-dependent potentiation of CEG renal toxicity. The CEG-induced renal
 lesion was dependent on a probenecid-sensitive transport system that was
 not involved in the toxicity of 2-bromohydroquinone. These studies
 demonstrate that CEG need not be metabolized by γ -
 glutamyltranspeptidase to the corresponding cysteine adduct
 [S-(2-chloroethyl)cysteine] in order to enter renal tubule cells and
 ultimately exert its nephrotoxic action.
 CT Medical Descriptors:
 *drug metabolism
 *nephrotoxicity
 rat
 intoxication
 kidney
 pharmacokinetics
 therapy
 intraperitoneal drug administration
 drug response
 histology
 nonhuman
 animal experiment
 animal cell
 dose response
 drug mechanism
 Drug Descriptors:
 *gamma glutamyltransferase
 *glutathione
 *acivicin
 *bromohydroquinone
 *s (2 chloroethyl)cysteine
 *s (2 chloroethyl)glutathione

*s (3,6 dioxo 1,4 cyclohexadienyl)glutathione
 glutathione derivative
 probenecid
 unclassified drug
 RN (gamma glutamyltransferase) 85876-02-4; (glutathione) 70-18-8; (acivicin) 42228-92-2; (probenecid) 57-66-9
 CN Acivicin

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 DICTIONARY FILE UPDATES: 21 JUN 2005 HIGHEST RN 852656-52-1

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 * available and contains the CA role and document type information. *
 *

Crossover limits have been increased. See HELP CROSSOVER for details.

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<http://www.cas.org/ONLINE/DBSS/registryss.html>

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L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 9046-27-9 REGISTRY
 ED Entered STN: 16 Nov 1984
 CN Glutamyltransferase, γ - (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN α -Glutamyltranspeptidase
 CN γ -Glutamyl peptidyltransferase
 CN γ -Glutamyl transpeptidase
 CN γ -Glutamyl transpeptidase-related enzyme
 CN γ -Glutamyltransferase
 CN γ -GPT
 CN γ -GT
 CN γ -GTP
 CN E.C. 2.3.2.2
 CN L- γ -Glutamyl transpeptidase
 CN L- γ -Glutamyltransferase
 CN L-Glutamyltransferase

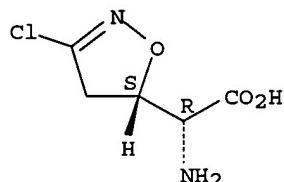
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 MF Unspecified
 CI MAN
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CABA,
 CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, CSNB, IFICDB, IFIPAT,
 IFIUDB, MSDS-OHS, NAPRALERT, NIOSHTIC, PROMT, TOXCENTER, USPAT2,
 USPATFULL
 Other Sources: EINECS**, TSCA**
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*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
 8426 REFERENCES IN FILE CA (1907 TO DATE)
 14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 8440 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d ide 18 tot

L8 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 676551-24-9 REGISTRY
 ED Entered STN: 23 Apr 2004
 CN 5-Isoxazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 (α R,5S)- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C5 H7 Cl N2 O3
 SR CA
 LC STN Files: CA, CAPLUS

Absolute stereochemistry.

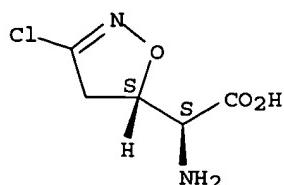


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L8 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 161922-40-3 REGISTRY
 ED Entered STN: 04 Apr 1995
 CN 5-Isoxazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C5 H7 Cl N2 O3 . Cl H
 SR CA
 LC STN Files: CA, CAPLUS
 CRN (42228-92-2)

Absolute stereochemistry.

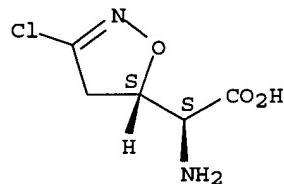


● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L8 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
 RN 105116-13-0 REGISTRY
 ED Entered STN: 08 Nov 1986
 CN 5-Isoxazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 monohydrochloride, (R*,R*)- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 5-Isoxazoleacetic acid, α -amino-3-chloro-4,5-dihydro-,
 monohydrochloride, (R*,R*)- (\pm) -
 FS STEREOSEARCH
 MF C5 H7 Cl N2 O3 . Cl H
 SR CA
 LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
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Relative stereochemistry.

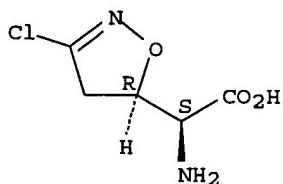


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 RN 104832-77-1 REGISTRY
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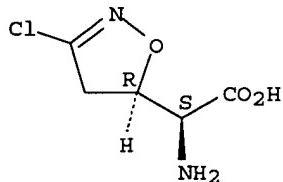


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RN 104832-76-0 REGISTRY
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Relative stereochemistry.

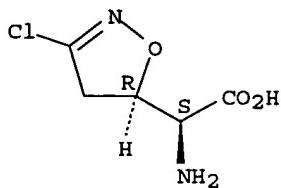


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(α S,5R)- (9CI) (CA INDEX NAME)
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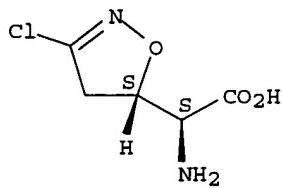


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RN 76898-56-1 REGISTRY
ED Entered STN: 16 Nov 1984
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(9CI) (CA INDEX NAME)
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(R*,R*)--(±)-
OTHER NAMES:
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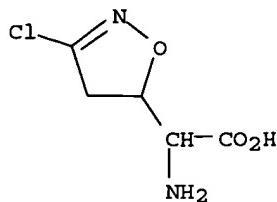
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INDEX NAME)
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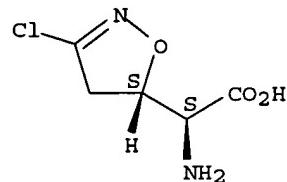


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 (α S,5S)- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
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 OTHER NAMES:
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 CN Antibiotic AT 125
 CN AT 125
 CN NSC 163501
 CN U 42126
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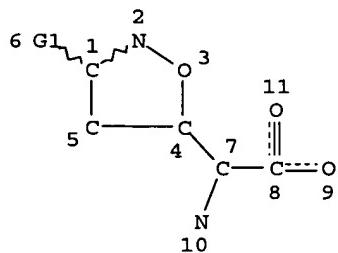
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STEREO ATTRIBUTES: NONE

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L30 ANSWER 21 OF 51 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN DUPLICATE

1

ACCESSION NUMBER: 2002-20395 DRUGU T P B

TITLE: Transmembrane proteases as disease markers and targets for therapy.

AUTHOR: Antczak C; de Meester I; Bauvois B

CORPORATE SOURCE: INSERM; Inst.Curie; CNRS; Univ.Antwerp

LOCATION: Paris, Fr.; Wilrijk, Belg.

SOURCE: J.Biol.Regul.Homeostatic Agents (15, No. 2, 130-39, 2001) 1

Fig. 3 Tab. 101 Ref.

CODEN: JBRAER ISSN: 0393-974X

AVAIL. OF DOC.: Unite 365 INSERM, Institut Curie, 26 Rue d'Ulm, 75231 Paris Cedex 05, France. (email: brigitte.bauvois@curie.fr). (B.B.).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

ABEX TMP are found in many normal and abnormal cells, and include neutral endopeptidase, ACE, aminopeptidase-N, aminopeptidase-A, dipeptidyl peptidase IV and gamma-glutamyl transpeptidase. Inhibitors include phosphoramidon, thiorphphan, retrothiorphphan, omaprilat, Z-13752A, SA-7060, captopril, enalapril, fosinopril, fasidotril, lisinopril, moexipril, quinapril, ramipril, trandolapril, actinonin, amastatin, ubenimex, probestin, PC-18, EC-27, EC-33, **acivicin** and anthglutin.

Clinically inhibitors can reduce hypertension, **diabetic nephropathy** and tumor growth; in animals inhibitors can affect tumors, cardiovascular system, immunity and nervous tissue; in-vitro inhibitors affect apoptosis, immunity and cell function. Systemic administration of inhibitors may cause toxicity; some are not specific to abnormal tissue. Inhibitors are needed that are not toxic, are highly specific and can be delivered locally to the disease site. An example of this is ADEPT, where a fusion protein of CD20 antibody and beta-glucuronidase activates the doxorubicin glucuronide prodrug in Daudi lymphoma cells. (YC)

CT [02] NEOPLASM *TR; ANIMAL-NEOPLASM *OC; HYPERTENSION *TR; DIABETIC *TR; NEPHROPATHY *TR; VASCULAR-DISEASE *TR; PHOSPHORAMIDON *PH; THIOPHAN *PH; RETROTHIOPHAN *PH; OMAPRILAT *PH; Z-13752A *PH; SA-7060 *PH; CAPTOPRIL *PH; ENALAPRIL *PH; FOSINOPRIL *PH; FASIDOTRIL *PH; LISINOPRIL *PH; MOEXIPRIL *PH; QUINAPRIL *PH; RAMIPRIL *PH; TRANDOLAPRIL *PH; ACTINONIN *PH; AMASTATIN *PH; UBNIMEX *PH; PROBESTIN *PH; PC-18 *PH; EC-27 *PH; EC-33 *PH; **ACIVICIN** *PH; ANTHGLUTIN *PH; DOXORUBICIN *PH; EC-3.4.24.11 *FT; EC-3.4.15.1 *FT; EC-3.4.11.2 *FT; EC-3.4.11.7 *FT; EC-3.4.14.5 *FT; EC-2.3.2.2 *FT; IMMUNITY *FT; HEART *FT; VESSEL *FT; KIDNEY *FT; TUMOR-CELL *FT; CYTOSTATIC *FT; HYPOTENSIVE *FT; KIDNEY-BRUSH-BORDER-NEUTRAL-PROTEINASE *FT; NEPRILYSIN *FT; NEUTRAL-ENDOPEPTIDASE *FT; DIPEPTIDYL-CARBOXYPEPTIDASE *FT; ACE *FT; AMINOPEPTIDASE *FT; ASPARTATE-AMINOPEPTIDASE *FT; DIPEPTIDYL-PEPTIDASE-IV *FT; GAMMA-GLUTAMYLTRANSFERASE *FT; TISSUE-CULTURE *FT; TR *FT; PH *FT

(Table 1). As compared to the corresponding Mpv17^{+/+} kidneys, no significant difference in glutathione levels and in the activities of superoxide dismutase (SOD), catalase, GSSG reductase and glutathione transferase (GST) was observed in the kidneys of both mouse strains. However, in kidneys of Mpv17^{-/-} mice γ -glutamyl transpeptidase (γ -GT) activity was increased by about two-fold, whereas glutathione peroxidase (GPx) activity was decreased by about one-third as compared to Mpv17^{+/+} animals. The following table illustrates the results:

TABLE 1 Enzyme activities in kidneys of Mpv17^{-/-} and Mpv17^{+/+} 7 - 9 months old mice

	Mpv17 ^{-/-}	Mpv17 ^{+/+}
mmol/g of kidney wet weight		
GSH	2.19 ± 0.28 (93) ^{a)}	2.35 ± 0.35
U / mg of protein		
Superoxide Dismutase	17.1 ± 1.6 (102)	16.7 ± 0.8
Catalase	381 ± 25 (88)	431 ± 16
nmol/min per mg of protein		
Glutathione Peroxidase	176 ± 12 (68)	259 ± 16
GSSG Reductase	98 ± 10 (85)	115 ± 10
Glutathione Transferase	508 ± 52 (98)	520 ± 36
γ - Glutamyl Transpeptidase	2,330 ± 295 (197)	1,180 ± 70

Data are given as means ± SEM (n= 10 animals)

^{a)} % of Mpv17^{+/+}

Example 4: Mpv17 dependent activities of γ -glutamyl transpeptidase and glutathione peroxidase in fibroblasts

Changes of enzyme activities determined in kidneys of Mpv17^{-/-} mice were similarly observed when in cultured Mpv17^{-/-} (LUSVX) cells were compared to Mpv17 expressing (NIX15) cells (Table 2). Most prominently, in Mpv17^{-/-} cells the activities of γ -GT were elevated by about six-fold, whereas the activities of GPx were lowered by one-third. The similarity in the change of γ -GT and GPx activity measured in Mpv17^{+/+} and Mpv17^{-/-} kidney and fibroblast culture suggests that these alterations occur at the cellular rather than the organismal level. The following table summarizes the results:

TABLE 2 Enzyme activities in LUSVX and NIX15 fibroblasts

	LUSVX (Mpv17 negative)	NIX15 (Mpv17 expressing)
<u>U/mg of protein</u>		
Superoxide Dismutase (n=2)	10.7 (61) ^{a)}	17.6
Catalase	410 \pm 60 (87)	470 \pm 90
<u>nmol/min per mg of protein</u>		
Glutathione Peroxidase	53 \pm 5 (66)	80 \pm 7
γ -Glutamyl Transpeptidase	15 \pm 0.4 (600)	2.5 \pm 0.01

Data are given as means \pm SEM (n=3-4)

^{a)} % of NIX15

Example 5: Mpv17 dependent changes in mRNA expression in fibroblasts

mRNA levels of the γ -GT and GPx genes were examined by quantitative RT-PCR in Mpv17expressing (NIX15) and Mpv17-/ (LUSVX) cells respectively (see Figure 2A below). γ -GT specific mRNA was enhanced by about 2-fold in Mpv17-/ cells. The expression of cellular GPx (cGPx), plasma GPx (pGPx), phospholipid hydroperoxide GPx (PHGPx) and of the nonselenium dependent GPx (nsGPx) was investigated. In Mpv17-/ cells only pGPx expression was decreased by about 80% (Figure 2A), which is basically consistent with the alteration in the activity of GPx (see Tables 1 and 2 above). Predominantly, pGPx appears to account for the overall low GPx activity. Remarkably, the expression of PHGPx, an enzyme responsible for protection from phospholipid peroxidation (R. L. Maser, B. S. Magenheimer and J. P. Calvet (1994), *Journal of Biological Chemistry*, **269**, pp. 27066-27073), was unaffected on the mRNA level.

The three different mouse SOD genes (CuZnSOD, MnSOD, ecSOD) show lower expression in Mpv17-/ cells, consistent with the lower SOD activity measured (see Table 2 above). No significant difference of xanthine dehydrogenase/ xanthine oxidase (XO) was detected on the mRNA level between Mpv17expressing and Mpv17 nonexpressing cells (see Figure 2A).

Example 6: Inhibition of γ -glutamyl transpeptidase activity restores glutathione peroxidase activity in Mpv17-/ cells

An inverse regulation of the glutathione-utilizing enzyme activities γ -GT and GPx was observed in Mpv17-/ animals and cells (see Tables 1 and 2 above). Because Mpv17-/ cells produce increased superoxide, a presumed regulatory function of the superoxide anion was tested by growing Mpv17-/ cells (LUSVX) in the presence of the SOD mimic MnTBAP (Y. Noda, M. Kohno, A. Mori and L. Packer (1999), *Journal Biological Chemistry*, **269**, pp. 23471-23476) Neither γ -GT nor GPx activities were changed significantly (Table 3) indicating that superoxide appears to have no role in the regulation of γ -GT and GPx in this system. Conversely, when Mpv17-/ cells were grown in the presence of acivicin, an efficient inhibitor of γ -GT, GPx activity was increased by about 1.6-fold. Thus, enzyme activities may be dependent on each

other in a way that γ -GT downregulates the activity of GPx. This inverse effect was also detected at the level of stable mRNA, as γ -GT inhibition led to a significant increase of pGPx and SOD mRNA levels (see Figure 2B).

TABLE 3 Activity of glutathione peroxidase and γ -glutamyl transpeptidase
in Mpv17 $^{-/-}$ cells (LUSVX) in presence of MnTBAP or acivicin

	LUSVX	LUSVX + MnTBAP	LUSVX	LUSVX + acivicin
nmol/min per mg of protein				
Glutathione Peroxidase	25.0 \pm 1.0	26.1 \pm 0.6	33.1 \pm 1.3	53.5 \pm 2.0
		(104%) ^{a)}		(162%)
γ -Glutamyl Transpeptidase	0.99 \pm 0.02	0.94 \pm 0.03	0.96 \pm 0.02	not detectable
		(95%)		

Values are given as means \pm SEM (n=3)

^{a)} % of controls

Example 7: Regulation of γ -GT and pGPx expression

The examples as documented herein above illustrate the following:

a) Reactive oxygen species in Mpv17 $^{-/-}$ cells

Using the ESR method superoxide was detected as the ROS species released from Mpv17 $^{-/-}$ fibroblasts. Production and secretion of superoxide are lower in Mpv17 expressing as compared to nonexpressing Mpv17 $^{-/-}$ cells. These data are in line with the significance of ROS in the generation of glomerular injury (R. J. Johnson, D. Lovett, R. I. Lehrer, W. G. Couser and S. J. Klebanoff (1994), *Kidney International*,

45, pp. 352-359) and with an analysis of Mpv17^{-/-} kidneys and isolated glomeruli, in which antioxidants were successfully used for therapeutic intervention in Mpv17^{-/-} animals (C. J. Binder, H. Weiher, M. Exner and D. Kerjaschki (1999), *American Journal of Pathology*, **154**, pp. 1067-1075).

b) Activity and expression of oxidative enzymes

Activity and expression of enzymes involved in ROS and glutathione metabolism were determined in Mpv17^{-/-} mice kidneys and fibroblasts in culture. An increase in γ -GT activity and a decrease in GPx activity were observed in both, Mpv17^{-/-} kidneys and fibroblasts. In addition, a decrease in SOD activity was observed in Mpv17^{-/-} fibroblasts. At the mRNA level, a negative correlation between the expression of γ -GT and the expression of the GPx and the SOD genes was observed in Mpv17^{-/-} cells. All the three different SOD mRNAs tested were significantly decreased, but only the plasma GPx gene expression was strongly diminished, the latter presumably accounting for the decrease of GPx activity measured.

Negative correlations between the activity and expression of γ -GT and of enzymes involved in GSH and ROS metabolism have been reported earlier. Thus, inverse changes of GPx and γ -GT activities under the condition of oxidative stress were determined in rats exposed to cigarette smoke (C. V. Anand, U. Anand and R. Agarwal (1996), *Indian Journal Experimental Biology*, **34**, pp. 486-488) and in fetal mice exposed to alcohol (S. A. Amini, R. H. Dunstan, P. R. Dunkley and R. N. Murdoch (1996), *Free Radical Biology and Medicine*, **21**, pp. 357-365). Similarly, an inverse relationship of γ -GT and CuZnSOD expression has been noted recently in rat livers after iron poisoning (N. Taniguchi and Y. Ikeda (1998), *Advances in Enzymology and Related Areas of Molecular Biology*, **72**, pp. 239-278) But, in contrast to these previously described models, in the Mpv17 mouse model no chemical insult was applied.

c) Regulation of γ -GT and pGPx expression

In the absence of Mpv17 protein the γ -GT gene is upregulated while the mRNA level of pGPx is decreased. The mouse γ -GT gene is a single copy gene underlying intricate control mechanisms involving at least seven promoters (N. Taniguchi and Y. Ikeda (1998), *Advances in Enzymology and Related Areas of Molecular Biology*, **72**, pp. 239-278). The membrane-bound γ -GT is involved in regulating cellular redox potential and intracellular GSH levels (T. C. Nichols, J. M. Guthridge, D. R. Karp, H. Molina, D. R. Fletcher and V. M. Holers (1998), *European Journal of Immunology*, **28**, pp. 4123-4129). The activity of γ -GT can be increased by glutathione depletion (R. J. van Klaveren, P. H. Hoet, J. L. Pype, M. Demedts and B. Nemery (1997), *Free Radical Biology and Medicine*, **22**, pp. 525-534) or by hyperoxia (A. Kugelman, H. A. Choy, R. Liu, M. M. Shi, E. Gozal and H. J. Forman (1994), *American Journal Respiratory Cell and Molecular Biology*, **11**, pp. 586-592) in different systems.

pGPx is an extracellular peroxidase of the selenium-containing GPx family, using GSH as well as thioredoxin and glutaredoxin as thiol substrates (M. Björnstedt, J. Xue, W. Huang, B. Akesson and A. Holmgren (1994), *Journal of Biological Chemistry*, **269**, pp. 29382-29384). More abundant in kidney than in other tissues, pGPx is synthesized and secreted in the proximal tubules and in the glomeruli, consistent with its function in protecting kidney from extracellular oxidative damage (R. L. Maser, B. S. Magenheimer and J. P. Calvet (1994), *Journal of Biological Chemistry*, **326**, pp. 579-585; D. M. Tham, J. C. Whitin, K. K. Kim, S. X. Zhu and H. J. Cohen (1998), *American Journal of Physiology*, **275**, G1463-1471). Downregulation of pGPx as observed in Mpv17 $^{-/-}$ cells weakens the protection against extracellular oxidative insult.

The γ -GT activity in Mpv17 $^{-/-}$ cells controls the level of pGPx mRNA as γ -GT inhibition relieves this downregulation (Fig2b). This control might involve imbalanced levels of intra- or extracellular GSH or superoxide due to enhanced γ -GT activity, presumably mediated by the activation of superoxide responsive transcription factors such as NF- κ B or AP-1 (H. L. Pahl and P. A. Baeuerle (1994), *Bioessays*, **16**, pp.

497-502). However, superoxide removal does neither affect the γ -GT nor the GPx activity, arguing against superoxide as a regulator.

Several genes relevant to the development of the disease phenotype, i.e. MMP-2 and its regulator TIMP-2, have been shown to be upregulated in Mpv17^{-/-} mice earlier (A. Reuter, A. Nestl, R. M. Zwacka, J. Tuckerman, R. Waldherr, E. M. Wagner, M. Hoyhtya, A. M. Meyer zum Gottesberge, P. Angel and H. Weiher (1998), *Molecular Biology of the Cell*, **9**, pp. 1675-1682). Since antioxidant intervention is effective in phenotype prevention in our model (C. J. Binder, H. Weiher, M. Exner and D. Kerjaschki (1999), *American Journal of Pathology*, **154**, pp. 1067-1075), these alterations should be consequences rather than causes to ROS generation. By contrast, the data presented here suggest that overproduction of γ -GT in these animals is causal to elevated ROS levels (see below).

d) Origin of enhanced ROS levels in Mpv17^{-/-} mice

Enzymes most affected in Mpv17^{-/-} kidneys and cells, γ -GT and pGPx, both exert their enzymatic activity predominantly in the extracellular space. In particular, γ -GT expression and activity are enhanced in the absence of the Mpv17 function. Cells overproducing γ -GT should be efficiently protected against intracellular oxidative injury by increased supply of intracellular GSH. Extracellular GSH is metabolised by γ -GT to glutamate and cysteinylglycine which in contrast to GSH can directly enter cells and thus provide them with a source of cysteine (M. W. Lieberman, A. L. Wiseman, Z. Z. Shi, B. Z. Carter, R. Barrios, C. N. Ou, P. Chevez-Barrios, Y. Wang, G. M. Habib, J. C. Goodman, S. L. Huang, R. M. Lebovitz and M. M. Matzuk (1996), *Proceedings of the National Academy of Sciences of the U.S.A.*, **76**, pp. 5606-5610). The latter is present at lowest concentration of all amino acids and a limiting component for intracellular *de novo* GSH synthesis. Thus, γ -GT, localized at the luminal surface of the renal proximal tubules, plays a key role in cysteine and glutathione homeostasis in maintaining cellular GSH levels (A. Kugelman, H. A. Choy, R. Liu, M. N. Shi, E. Gozal and H. J. Forman (1994), *American Journal Respiratory Cell and Molecular Biology*, **11**, pp. 586-592).

At the same time, increased γ -GT activity might lead to a depletion of extracellular GSH and thereby weaken the resistance against extracellular ROS. In mice, however, this is unlikely, because plasma GSH levels are about 100-fold higher than in humans (O. W. Griffith and A. Meister (1979), *Proceedings of the National Academy of Sciences of the U.S.A.*, **76**, pp. 5606-5610), that is well above a critical substrate concentration for pGPx activity of <0.5 μ M (A. Wendel and P. Cikryt (1980), *FEBS Letters*, **120**, pp. 209-211). Instead, increased γ -GT activity may directly enhance superoxide in the Mpv17^{-/-} system. Such direct production of superoxide by γ -GT activity was recently demonstrated in an *in vitro* system containing GSH and transferrin as an iron source. It was shown that superoxide was generated by the reaction of the GSH breakdown product cysteinylglycine (R. Drozdz, C. Parmentier, H. Hachad, P. Leroy, G. Siest and M. Wellman (1998), *Free Radicals Biology and Medicine*, **25**, pp. 786-792). Superoxide can instantly undergo a Fenton type reaction to turn into the highly noxic hydroxyl radical, causing lipid- and protein peroxidation (R. Drozdz, C. Parmentier, H. Hachad, P. Leroy, G. Siest and M. Wellman (1998), *Free Radicals Biology and Medicine*, **25**, pp. 786-792). In vivo, hydroxyl radical generation and lipid peroxidation in the presence of metals and under conditions of enhanced γ -GT activity have been described earlier in rat liver (K. E. Brown, M. T. Kinter, T. D. Oberley and D. R. Spitz (1998), *Free Radical Biology and Medicine*, **24**, pp. 545-555; A. A. Stark, E. Zeiger, D. A. Pagano (1993) *Carcinogenesis*, **14**, pp. 183-189; A. Paolicchi, R. Tongiani, P. Tonarelli, M. Comporti and A. Pompella (1997), *Free Radicals Biology and Medicine*, **22**, pp. 853-860).

The above described experiments clearly demonstrate that γ -GT activity plays a key role in the generation of extracellular ROS. Recently, γ -GT upregulation has been reported to be causal to oxidation damage during short-term ischemia of rat kidney and this effect was inhibitable by acivicin (J. C. Cutrin, B. Zingaro, S. Camandola, A. Boveris, A. Pompella and G. Poli (2000), *Kidney International*, **57**, pp. 526-533). Thus, the use of γ -GT inhibitors provides a potent and useful treatment of ROS degenerated diseases and injuries in humans as well.

Mpv 17-/mice, i.e. mice of the glomerulosclerosis reference strains are treated, in accordance with this invention, by oral administration of 5 to 50 mg/kg activicin (AT-125) for several weeks. The protective use of activicin is analyzed by pathological methods and/or molecular means.

Claims

1. Use of γ -GT inhibitors for the preparation of a pharmaceutical composition for the treatment of a degenerative disease.
2. The use of claim 1, wherein said degenerative disease is a chronic renal disease or an inner ear degenerative condition or injury.
3. The use of claim 2 wherein said chronic renal disease is ROS induced.
4. The use of claim 3, wherein said chronic renal disease is selected from the group consisting of focal glomerulosclerosis, segmental glomerulosclerosis, minimal change nephrosis, inflammatory glomerulopathies, diabetic nephropathy and autoimmuno glomerulopathies.
5. The use of claim 2, wherein said inner ear injury is ROS induced.
6. The use of claim 5, wherein said ROS induced inner ear injury is sensineurial deafness induced by age, physiological status, metabolic status or drugs.
7. The use of claim 6, wherein said drugs are selected from aminoglycosides or cisplatin derivatives.
8. The use of claim 2, wherein said inner ear degenerative condition is otosclerosis.
9. The use of any one of claims 1 to 8, wherein said γ -GT inhibitor is selected from the group consisting of AT-125, Acivicin or its derivatives, γ -glutamyl amino acids and peptides of the general formula γ -Glu-XY, peptides of the general formula (CysGlyX), peptidomimetic glutathion analogues, compounds or derivatives of the type L-2-amino-4-boronobutanoic acid (ABBA), and anilides, such as γ -glutamyl-7-amido-4-methylcoumarin (γ -Glu-AMC).

10. The use of claim 9, wherein X and Y stand for any naturally occurring aminoacid, a modified aminoacid, a oligopeptide or a polypeptide.

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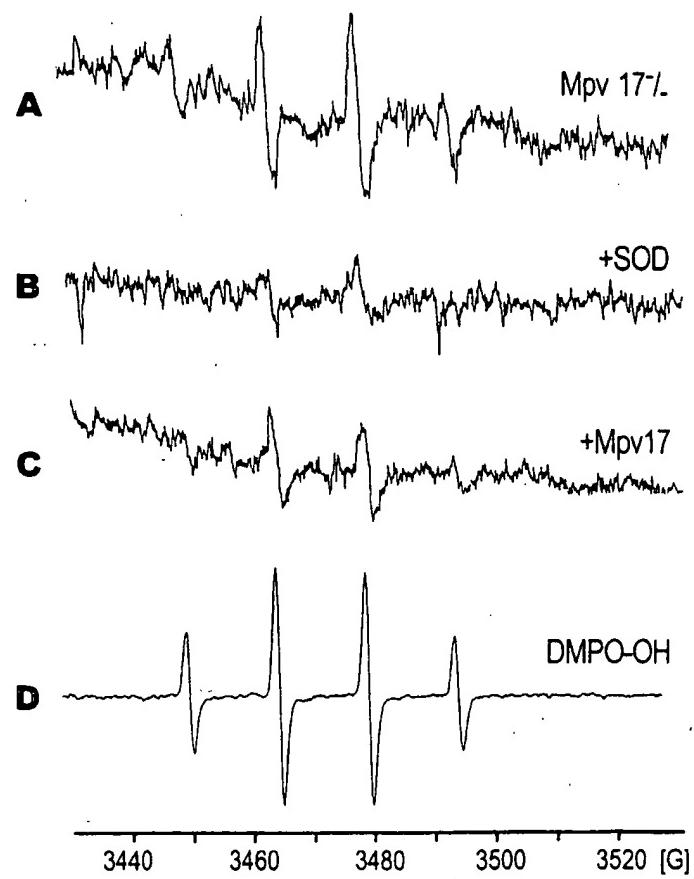


Fig. 1

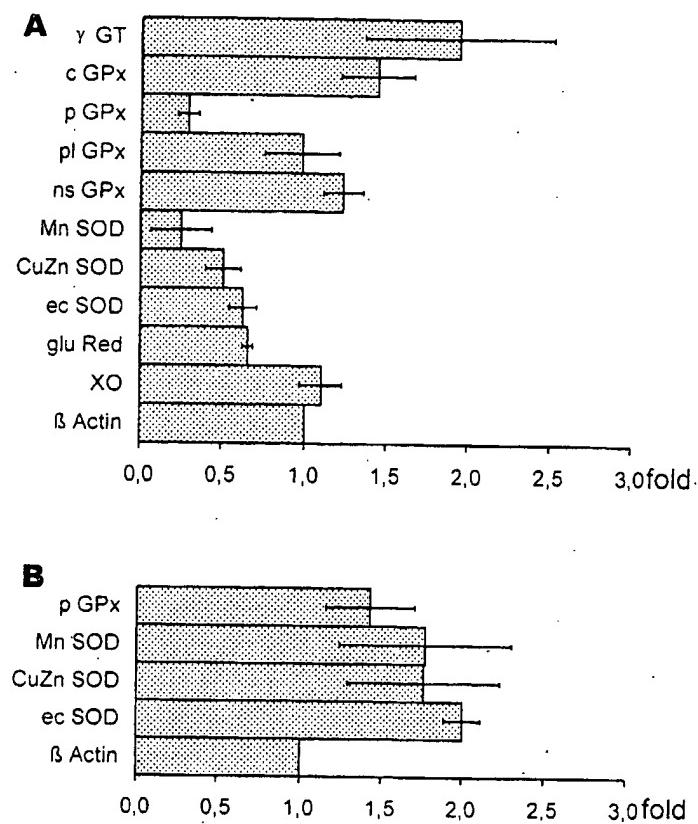


Fig. 2

INTERNATIONAL SEARCH REPORT

Internal	Application No
PCT/EP 02/01799	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K38/06 A61P27/16 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 758 551 A (MEISTER ALTON ET AL) 19 July 1988 (1988-07-19) cited in the application abstract; claims column 3, line 47 - line 63 column 2, line 47 - line 55 --- -/-	1-4, 9, 10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the international filing date
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- *'T' later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *'8' document member of the same patent family

Date of the actual completion of the international search

27 June 2002

Date of mailing of the international search report

22/07/2002

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INTERNATIONAL SEARCH REPORT

Internal	Application No
PCT/EP 02/01799	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TOWNSEND DANIELLE M ET AL: "In vivo metabolism of cisplatin to a nephrotoxin by gamma-glutamyl transpeptidase and beta-lyase." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 266 XP001084090</p> <p>91st Annual Meeting of the American Association for Cancer Research.; San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X abstract</p> <p>---</p>	1-4, 9
X	<p>HANIGAN M H ET AL: "Human germ cell tumours: Expression of gamma-glutamyl transpeptidase and sensitivity to cisplatin." BRITISH JOURNAL OF CANCER, vol. 81, no. 1, 1999. pages 75-79, XP001083693</p> <p>ISSN: 0007-0920 abstract</p> <p>page 79, left-hand column, paragraph 3 - paragraph 4</p> <p>page 75, left-hand column</p> <p>---</p>	1-4, 9
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; August 1998 (1998-08)</p> <p>HANIGAN MARIE H ET AL: "Expression of gamma-glutamyl transpeptidase in stage III and IV ovarian surface epithelial carcinomas does not alter response to primary cisplatin-based chemotherapy." Database accession no. PREV199800451043 XP002203802</p> <p>abstract</p> <p>& AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, vol. 179, no. 2, August 1998 (1998-08), pages 363-367, ISSN: 0002-9378</p> <p>---</p> <p>-/-</p>	1-7

INTERNATIONAL SEARCH REPORT

Intern	Application No
PCT/EP 02/01799	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EVANS P., HALLIWELL B: "Free radicals and hearing: cause, consequence and criteria" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 'Online!', vol. 884, no. 1, 1999, pages 19-40, XP002203800</p> <p>Retrieved from the Internet: <URL:www.annalsnyas.org> 'retrieved on 2002-06-27'</p> <p>"Interaction of drugs with reactive oxygen species"</p> <p>---</p>	1,2,5-7, 9
X	<p>LOPEZ-GONZALEZ MIGUEL A ET AL: "Ototoxicity caused by cisplatin is ameliorated by melatonin and other antioxidants." JOURNAL OF PINEAL RESEARCH., vol. 28, no. 2, March 2000 (2000-03), pages 73-80, XP002203801</p> <p>ISSN: 0742-3098</p> <p>page 73</p> <p>---</p>	1,2,5-7, 9
X	<p>DATABASE BIOSIS 'Online!' BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1996</p> <p>NISHIDA ISAO ET AL: "Attenuation of aminoglycoside ototoxicity by glutathione." Database accession no. PREV199699048528</p> <p>XP002203803</p> <p>abstract</p> <p>& ORL (BASEL),</p> <p>vol. 58, no. 2, 1996, pages 68-73,</p> <p>ISSN: 0301-1569</p> <p>---</p>	1,2,5-7, 9
A	<p>KIL J ET AL: "Localization of gamma-glutamyl transpeptidase in the chick inner ear sensory epithelia." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 22, no. 1-3, 1996, page 1621</p> <p>XP001083810</p> <p>26th Annual Meeting of the Society for Neuroscience; Washington, D.C., USA;</p> <p>November 16-21, 1996</p> <p>ISSN: 0190-5295</p> <p>abstract</p> <p>----</p>	1-9

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 02/01799

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4758551	A 19-07-1988	NONE	

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DUPLICATE

ACCESSION NUMBER: 2000:30048831 BIOTECHNO
TITLE: Bioartificial kidney for full renal replacement therapy
AUTHOR: Humes H.D.
CORPORATE SOURCE: Dr. H.D. Humes, Department of Internal Medicine, Univ. of Michigan Medical Center, Ann Arbor, MI 48109, United States.
E-mail: dhumes@umich.edu
SOURCE: Seminars in Nephrology, (2000), 20/1 (71-82), 79 reference(s)
CODEN: SNEPDJ ISSN: 0270-9295
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
CT *erythropoietin; *artificial kidney; *chronic kidney disease; *acute kidney failure; ouabain; phlorizin; 4 aminohippuric acid; acivicin; colecalciferol; parathyroid hormone; probenecid; gene therapy; genetic engineering; mortality; morbidity; blood filter; continuous ambulatory peritoneal dialysis; hemofiltration; kidney tubule absorption; ammonia formation; biosensor; human; review; priority journal
RN (erythropoietin) 11096-26-7; (ouabain) 11018-89-6, 630-60-4; (phlorizin) 60-81-1, 7061-54-3; (4 aminohippuric acid) 61-78-9; (acivicin) 42228-92-2; (colecalciferol) 1406-16-2, 67-97-0; (parathyroid hormone) 12584-96-2, 68893-82-3, 9002-64-6; (probenecid) 57-66-9